Ilse Hofmeester

NIGHT-TIME VOIDING DISORDERS

enuresis and nocturia
in adolescents and adults

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Abbreviations

Adapted DBT	–	Adapted Dry Bed Training
AD(H)D	–	Attention Deficit (Hyperactivity) Disorder
ASD	–	Autism Spectrum Disorder
AVV	–	Average Voided Volume
CI	–	Confidence Interval
DBC	–	Dry Bed Center
EBC	–	Expected Bladder Capacity
FMV	–	First Morning Void
FVC	–	Frequency Volume Chart
ICCS	–	International Children's Continence Society
ICS	–	International Continence Society
IQR	–	Interquartile Range
LUTS	–	Lower Urinary Tract Symptoms
MNE	–	Monosymptomatic Nocturnal Enuresis
MBV_{flow}	–	Maximum Bladder Volume, as measured by adding voided volume of uroflowmetry and PVR
MVV	–	Maximum Voided Volume
MVV_{fvc}	–	Maximum Voided Volume, as measured by FVC
NMNE	–	Non Monosymptomatic Nocturnal Enuresis
NP	–	Nocturnal Polyuria
NPi	–	Nocturnal Polyuria index
OR	–	Odds Ratio
PVR	–	post voiding residue
Qmax	–	maximum urinary flow rate in ml/sec

CHAPTER 1

General introduction and outline of the thesis

Parts of this chapter have been submitted as a book chapter on nocturnal polyuria, to be published in: Drake, Lower Urinary Tract Symptoms in Adults, Springer, 2017

This thesis studies different aspects of enuresis and nocturia, in order to provide a more united view of these two related conditions. To understand current insights and treatment modalities, history may be helpful. This introduction starts with subsections on enuresis and on nocturia and moves on to the underlying pathophysiological concepts of both conditions: nocturnal polyuria (NP), small bladder capacity and sleep problems. Finally, the general aims and outline of this thesis are described.

Enuresis

More than 3000 years of history

Enuresis is derived from the Greek word ἐνούρησις, meaning to urinate in the night (nocturna), or in plain English: bedwetting. Enuresis has been referred to on the earliest papyrus documents found (1550 BC). It is clear that is has always been a shameful symptom, which led to lower assumed physical and intellectual abilities, accuse of laziness and lack of hygiene [1], and sorrow in parents [2]. The problem of enuresis was treated with physical punishment and magical or religious treatments and ceremonies [1, 2]. Salmon described a very compact and compelling history of treatment for bedwetting, from the earliest days of mankind onwards [2]. Treatments are vividly described; like the following in the first (1545) British textbook of Thomas Phair: *"Take the wesande of a cocke and pluck it, tha brenne it in pouder and vse it twyse or thryse a daye. The stones of a hedgehogge poudred is of the same vertue. Item the clawes of a goate..." [2].* Or, in modern English: *'take the esophagus of a rooster and harvest it. Burn it to powder and use it twice or three times a day. The powder of an hedgehogs insides works as well. Collect the claws of a goat'.*

Several doctors, like Bagellardus and Rhazes followed the dogma of humors [2, 3]. Enuresis was often seen as a sign of the devil or as laziness. However, mainly in rural areas, it was accepted to wait for puberty to stop the problem, as the dirty bed straw was easily disposed with the animal excrements [1]. Towards the nineteenth century, urbanization with its associated increased hygiene requirements and few washing facilities- the crisis of filth- [4], made the enuretic an easy outcast [1]. Therefore, in the eighteenth century, different hypotheses were formed, like extreme irritable, weak or small bladder, or a meatus that was insensitive [1]. Several chemical and mechanical treatments were tried [2].

In the second half of the nineteenth century (the Victorian era), mother and child received better medical care, especially due to the aforementioned urbanization. Also, enuresis was a problem in the army. Enuresis patients were subjected to a combination of the following treatments: "fluid restriction, enemata, the use of an alarm clock, cold baths, warm baths, cold dashes to the perineum, douches to the lower spine" and all kind of mixtures of drugs, applied orally, rectally or as an ointment, injected in the perineum, into the meatus or the whole urethra [2]. Mechanical treatments were used to try to stop the urine from flowing, by compressing the urethra or closing the meatus, like a tape or iron device around the penis [1, 2].

Remarkably, in 2013 a case report was published about an eight year old boy suffering from penile Tourniquet syndrome, due to applying a thread around his penis for 15 days to try to stop his enuresis [5], expressing the same rationale as these mechanical devices, and showing the possible damage. This was noticed by several physicians in those days as well [2].

The current frequently applied alarm therapy has two interesting predecessors in the Victorian civilized and in the tribal world. The first is an electrical apparatus that was used at night with a moist sponge between the shoulders and a dry one over the meatus. When wetting occurred, the electrical circuit was completed and the patient arose. The second is a frog, tied to the belly of the patient, which croaked when wetting occurred, waking the patient as well [2].
In the twentieth century, discussion arose whether or not enuresis was a psychosocial problem alone, and the MacDonald triad of enuresis, fire setting and animal abuse was described [6, 7]. Since the last decades of the twentieth century, enuresis is thought to have a multifactorial origin [8], and several treatment modalities became available.

Terminology

When searching Pubmed for enuresis, the results encountered show that the definition has changed over time [8, 9]. The first three quarters of the twentieth century, enuresis was not only intermittent incontinence (at night) [8, 10]. Enuresis could mean 'enuresis risoria (giggle incontinence)', 'enuresis ureterica' (ectopic ureter causing continuous incontinence), diurnal enuresis or nocturnal enuresis. The last change in terminology was made in 2006 by the International Children's Continence Society (ICCS) [11]. This report was updated in 2014 [8]. Enuresis currently is defined as nighttime intermittent incontinence (Figure 1). The addition of the term 'nocturna' is optional. Daytime incontinence is the term for incontinence during the day, and the term diurnal enuresis should be avoided [12]. In this thesis, this current definition of enuresis is used: nighttime intermittent incontinence of ≥ 1 episode per month. Enuresis is subdivided in monosymptomatic (MNE) and non-monosymptomatic enuresis (NMNE), the latter including daytime Lower Urinary Tract Symptoms (LUTS). Individuals with secondary enuresis have experienced a dry period of at least six months, those with primary enuresis have not.

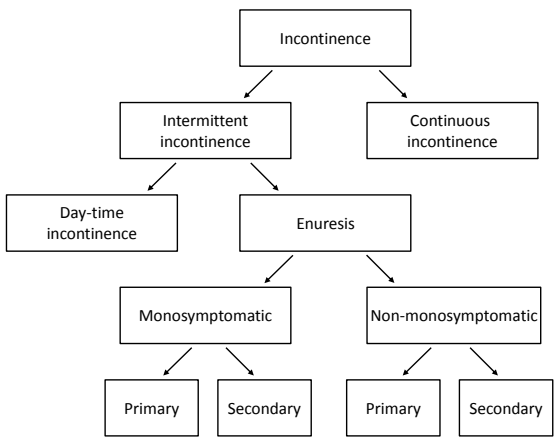

Figure 1. Definition of enuresis. Adapted from Austin 2014 [8].

Pathophysiology and etiology

Enuresis has a multifactorial origin and has been found to be related with several genetic, physiologic and psychologic factors [13]. A genetic and clinical heterogeneity is apparent: several loci on different chromosomes are involved in enuresis: chromosome 8, 12, 13 and 22 [14-19]. Enuresis is associated with several diseases, like sickle cell disease [20], constipation [21], sleep apnea and upper airway obstructive symptoms [22] and prior cardiac [23] and renal [24] transplantation. It can also arise in patients with an orthotopic neobladder after radical cystoprostatectomy [25]. Psychological and behavioral disorders are present in 20-40% of children with enuresis. This includes both internalizing psychological disorders like depressive and anxiety disorders, and externalizing disorders like Attention Deficit (Hyperactivity) Disorder (AD(H)D and Oppositional Defiant Disorder (ODD) [26]. Behavioral problems do more frequently occur in secondary enuresis [8]. Treating the behavioral disorder can result in decrease of bedwetting as well. Psychopathology in enuresis seems to be associated with older age, male gender, low socio-economic status and admission to specialized clinics [27]. Additionally, enuresis can be medically induced, due to valproate [28], risperidone [29, 30] or lithium [31].

Current consensus is that enuresis results as an interaction of three causal factors: nocturnal polyuria, small bladder capacity and arousal disorders [32]. Enuresis patients were found to excrete less vasopressin at night than during the day, in contrast to children without enuresis [33], resulting in a larger nocturnal urine output. Age affects bladder storage, also in incontinent children [34]. Even in healthy children without enuresis undergoing fluid challenge, if the nocturnal urine production exceeds the bladder capacity, incidental wetting of the bed will be provoked [35]. The three causal factors are more extensively discussed later in this chapter.

Epidemiology

Since the late nineties, in several countries epidemiological surveys have been carried out. Most of them used parental questionnaires for school-aged children. Prevalence of nocturnal enuresis is lower in females and decreases with age. It is less prevalent in Asian countries (7-12 yrs. 8% [36], 5-15 yrs. 3.9'% [37], 16-40 yrs. 2.3% [38], whereas the numbers for Western countries and Africa seem comparable- Africa 6-16 yrs. 8-17.6% [39-41], North America: 5yr olds: 33%, 8 yr. olds: 18%, 11 yr. olds 7%, 17 yr. olds 0.7% [42], Australia 5-12 yr. olds: 18.9% [43]. In the Netherlands enuresis was found in 15% of 5-6 yr. olds and 1% of 13-15 yr. olds [44]. In a cross-sectional sample of 18-64 year old adults, enuresis prevalence was 0.5%. There were no significant differences between age groups nor gender [45]. The spontaneous remission rate in 1129 enuretic patients was 15% per year [46].

Effects on quality of life

Enuresis can cause stress and social problems [1, 47, 48], like bullying [49]. It affects self-esteem [45, 50, 51], and complicates holidays and relationships [45]. Constant poor-quality sleep can cause daytime sleepiness, depression and immune problems [52]. When properly treated, self-esteem may be normalized [51] and psychosocial damage can be prevented [53]. In contrast, those patients who remain wet if they grow older, have more severe complaints [54]. Enuresis also negatively affects the health related quality of life of patients and parents [55]. Still in the beginning of the twenty-first century, many parents in the US did not know that primary

nocturnal enuresis is a physical problem, and many healthcare providers never or rarely discussed enuresis, according to parents' responses [56]. Parental punishment for enuresis is now known to have a detrimental effect on depression and quality of life of children [57].

Treatment

Recent standardization documents on the treatment of enuresis state the following evaluation and treatment options for MNE [10] and NMNE [58]. Primary evaluation and treatment of MNE can be carried out by a primary care doctor or by an educated nurse, and should include a good history and a frequency volume chart (FVC). Treatment includes bladder advice (urotherapy), alarm therapy and/or desmopressin. Alarm therapy is in favor in case of small bladder capacity, desmopressin in case of nocturnal polyuria. If therapy-resistance is present, patients should be referred to a specialist, where anticholinergics or in specific cases, imipramine can be prescribed [10]. For NMNE, it is important to treat constipation, fecal incontinence and underlying lower urinary tract diseases symptoms (overactive bladder, postponement, dysfunctional voiding) first. Accompanying behavioral disorders should also be treated. If enuresis still persists afterwards, then the standard treatment, as described for MNE can be started [58]. Underneath, a short description of the different treatment modalities is given.

Alarm therapy has been introduced in 1938 by Mohrer and Mohrer, two psychologists, as a conditioning method [59, 60]. It works by achieving arousal to the sensation of a full bladder, and inhibit voiding. Most probably, it works by operant conditioning [60, 61]. Throughout the years, several different forms of alarm treatment have been investigated, like the pad and bell, the body sensor and alarm, and the body worn alarm. Overall, they all work by the rationale that, when the material between two electrodes or sensors will turn wet, and the circuit is closed, this leads to an alarm going off, making a sound or vibrating [60]. Alarm therapy has a high success rate (65%), although studies are heterogeneous in terms of inclusion and outcome parameters [62, 63]. It has a lower relapse rate (46%) than desmopressin (65%) [64]. Additionally, it has a positive effect on bladder storage in MNE [65].

Imipramin is a tricyclic antidepressant drug. The working mechanism is thought to be via the brainstem through noradrenergic action [66-68]. However, it had some unexpected adverse effects, like cardiac problems, personality changes, insomnia, anorexia and anxiety [68, 69], which made it a less favorable treatment option. Recently, it undergoes a slight comeback, as it has been propagated to be of use in therapy-resistant cases [10].

Another important current treatment is desmopressin, a synthetic vasopressin analogue. The working mechanism of arginine vasopressin peptide (AVP), which is formed in the pituitary gland, is discussed in the subsection on nocturnal polyuria. Desmopressin acts on the renal collecting duct and distal tubules to enlarge reabsorption of water and is a stronger antidiuretic than AVP itself [66]. Being introduced as a nasal spray, later and current routes of administration are oral tablets and an oral lyophylysate (sublingual melting) [70]. Efficacy was similar [71], or even better (probability improvement bedwetting odds ratio 2.0 (95%CI 1.07–3.73) of melt vs tablet) [70] In this mainly pharmacy-driven study, melt and tablet were given in a cross-over design to patients that were

already treated by desmopressin in advance. The overall prevalence of success (full response) was 19%. Therefore, the relative risk that this OR represents is lower - as explained in Chapter 2 – and is 1.68 (1.06-2.46). Desmopressin seems to increase patient compliance [70], although not significantly [71]. Response rates of desmopressin were reported to be similar to imipramine, but desmopressin gave fewer side-effects [72]. The most recent, 2009 Cochrane review shows that desmopressin, during treatment effectively reduced bed-wetting compared with placebo: relative risk (RR) for failure to achieve 14 dry nights with 20 µg was 0.84 (95%CI 0.79-0.91), mean difference in wet nights per week was -1.34 (95%CI -1.57- -1.11) [64]. However, desmopressin has a high relapse rate after stopping treatment, resulting in no difference after treatment has finished [64]. Structured withdrawal was recently reported to give lower relapse rates [73, 74]. Main side effects are anorexia, bad taste, headache, nasal discomfort, nosebleeds, rash, dermatitis, edema, sight problems and vomiting. The nasal problems are mainly noted for the nasal spray [64, 75]. For all administration routes, severe hyponatremia, with convulsions and coma, is a rare but serious complication [76, 77]. Predictive factors for severe hyponatremia to occur are excessive intake of fluids, younger age, start of therapy and prodromal symptoms like nausea, vomiting and headache [76, 78].

Urotherapy has a standard and a specific intervention component and is described in detail in the standardization document of the ICCS [8]. In short, it consists of LUT rehabilitation; a conservative therapy, including information and demystification, behavioral modification, life style advice on fluid intake and diet, registration of symptoms and voiding habits, and support and encouragement. Specific interventions include pelvic floor muscle training, neuromodulation, intermittent catheterization and cognitive behavioral therapy [8].

Dry Bed Training (DBT) has been developed by Azrin, Sneed and Fox in 1973 for retarded adults, and has been adjusted for non-retarded children with enuresis in 1974 [79]. It consists of alarm training, with several additional training components to obtain a faster result: hourly awakenings, large fluid intake to increase the desire to urinate, positive practice and cleanliness training, and positive reinforcement for correct urinations at the toilet. Positive practice involves getting out of bed to go to the toilet 20 times before sleeping, and after every wet episode. Cleanliness training involves changing bed sheets and night clothes in case of a wet bed, by the child itself. The training was performed by parents, at home, except for the first intensive training night, in which an outsider did the training at home. The first night included all elements described above. During the following nights, only positive practice and cleanliness training were performed, and children were woken at their parents' bedtime to go to the toilet; every day this was half an hour earlier. After seven consecutive dry nights, the training was stopped. This method appeared to be rapid and effective. Bollard adjusted the training by teaching the parents to administer the whole procedure, including the first training night; lowering expenses and inconvenience of an outside trainer at home [80]. To reduce expenses even more, training parents in groups was performed, which was shown to be as effective as individual parent training [81]. Two-year follow-up of 60 children treated by DBT showed that after achieving dryness during a fortnight, 39% of the group relapsed during the two years of follow-up. After re-treatment with DBT, 14 out of 15 cases were dry [82]. Evidence suggested that the alarm could be left out as well, although results were not as good

[83]. In Butlers Modified DBT (DBT-M), the positive practice and the reprimands were left out [83]. The 2008 Cochrane review on complex behavioral interventions for enuresis stated that a complex intervention like DBT including an alarm was better than no treatment and than alarm treatment alone. The effect of only DBT without an alarm was not better than an alarm on its own. Direct contact and support from a therapist might increase the effect of the intervention [84].

Several other treatments have been reported, like furosemide [85], bladder transection [86], acupuncture [87] and hypnotherapy [88], although reports are of low quality [87].

Nocturia

History

Nocturia is derived from the Greek word νυκτουρία, merging the words for night and for urine. Although mankind has probably experienced nocturia as a symptom since ancient history, historical reports on nocturia are not easily found. In contrast to the history of enuresis, until the beginning of the twenty-first century, nocturia has mainly been described as one of the Lower Urinary Tract Symptoms (LUTS), as part of or associated with different disease entities. Nocturia is only investigated as a sole symptom or condition since the last decades. It gains more and more attention by urologists and general practitioners and is discussed in focus groups of the ICS [89, 90]. Nocturia was initially thought to be mainly a condition in men. However, we now know that it is as prevalent in women [91, 92].

Terminology and effects on quality of life

The most recent terminology report of nocturia was published by the ICS in 2002 [93]. Nocturia is defined as the number of voids during a night sleep; each void is preceded and followed by sleep [93]. It is distinct from night-time frequency, which is defined as the number of voids recorded from the moment an individual goes to bed with the intention of sleeping until the moment an individual wakes with the intention of rising [93]. In general, nocturia is known to be clinically bothersome if a person experiences two or more voids during sleep. However, some people experience one void to be bothersome and others are not bothered by three, or even more, nocturnal voids. Nocturia may affect health and well-being [94] and is associated with several morbidities like falling and fractures [95]. Nevertheless, in 2007, there was still a lack of knowledge on nocturia in patients [96].

Pathophysiology and etiology

Just like enuresis, nocturia is known to be multifactorial. Several symptoms and conditions are assumed to be associated with nocturia, although some are just co-occurring with increasing age. Examples are: body mass index, Hispanic and Black race, diabetes, hypertension, anxiety and depression, a history of enuresis, arthritis, asthma, heart disease, inflammatory bowel disease, cystitis, uterine prolapse, hysterectomy, menopausal status, prostatitis and prostate cancer [97], as well as obstructive sleep apnea syndrome (OSAS) [98]. Additionally, nocturia may be part of the Over Active Bladder (OAB) syndrome.

Causal factors of nocturia are nocturnal polyuria, global polyuria, bladder storage problems, sleep problems and circadian clock problems [93, 99], which all have their own causes [100]. Global polyuria, which represents the condition in which the 24-hour urine production exceeds 40 ml/kg bodyweight, is found in conditions like diabetes mellitus, diabetes insipidus, behavioral excessive fluid intake or it can be a side effect of medication [99]. The other factors will be described more extensively further on, as they are causal factors in enuresis as well.

Epidemiology

The prevalence of nocturia in the general population is high. In a large cross-sectional survey in 30,000 men and women of the general population with a 59% response rate, nocturia (≥1x) was present in 69% of men and 76% of women. Clinically relevant nocturia (≥2x) was present in 28% and 34% [97]. Other studies give comparable, or slightly lower, numbers [91]. In the Netherlands, in men aged 50-78 years from the general population, nocturia (≥2x) prevalence was 27.1% [101]. Important to note is that the prevalence of nocturia may differ depending on the assessment method used; questionnaires like the International Prostate Symptom Score, or FVCs [102, 103]. Most often, prevalence of nocturia is described, which is the proportion of cases in a population on a specific moment in time. The incidence rate – the number of new cases in the population that is at risk, in a given time period – is rarely investigated, but was found to be 23.9% in a Dutch longitudinal study in men aged 50 to 78 years [102].

Treatment

Treatment of nocturia depends on its main cause [89, 100]. Therefore, a thorough evaluation by means of an FVC is necessary [99]. The optimal length of an FVC seems to be 3 days, at the optimal balance of patient compliance and reliability [104]. The European Association of Urology (EAU) 2015 guideline on non-neurogenic male LUTS reports a flow chart in which treatment is described in a stepwise manner [105]. A recent report on the proceedings of specific nocturia sessions of the International Consultation on Incontinence - Research Society (ICI-RS) recently also proposed an algorithm for the treatment of nocturia [89].

In general, the following treatments are advised for the separate causes. In case of 24-hour polyuria, Diabetes Mellitus should be treated, intake should be reduced, and desmopressin could be considered according to the ICI-RS. In case of NP, the EAU states that education and lifestyle advice should be given, with or without desmopressin. The ICI-RS additionally mentions furosemide and treatment of OSAS. Additionally, drugs possibly causing nocturia or NP should be assessed first. In case of predominant bladder storage problems, the EAU propagates education and lifestyle advice, with or without a muscarinic receptor antagonist, although the effectivity of this drug is questionable. If storage problems are not predominant and prostate volume is larger than 40 ml, education, life-style advice, 5 α-reductase inhibitor and α-blocker or PDE5 inhibitor can be prescribed, drugs of which the effectivity is not certain either. The ICI-RS is quite in line and reports that in case of bladder storage problems due to Bladder Outlet Obstruction (BOO), α-blockers, 5-α-reductase inhibitors, pelvic floor muscle exercises or desobstruction are treatments of choice. For bladder storage problems due to overactive bladder (OAB) or detrusor over activity (DO), treatment consists of an anticholinergic, pelvic floor muscle exercises, β-3 agonist, sacral neuromodulation or botulinum

toxin injection submucosally in the bladder [89].

As discussed, both nocturia and enuresis are thought to share the causes of 24-hour polyuria, nocturnal polyuria, small bladder capacity and sleep problems, and circadian clock problems. The following paragraphs will focus on these.

Nocturnal polyuria

Nocturnal polyuria is the condition of overproduction of urine at night.. Physiologically, several renal mechanisms regulate urine production. In specific, atrial vasopressin (AVP) – or antidiuretic hormone (ADH)- changes renal excretion of water and regulates plasma osmolality and sodium concentration. This hormone is formed in the paraventricular and supraoptic nuclei of the hypothalamus and is released from the pituitary gland, in response to increased plasma osmolality or low blood pressure and blood volume. The vasopressin-2 (V2) receptor subtype is most important for antidiuresis and is located in the epithelial cells of the renal collecting duct. The other less important subtypes (V1a and V1b) are located in the vascular and central nervous system. When AVP is absent, the thin epithelial membrane between urine and blood in the renal collecting duct is almost impermeable to water. In the presence of AVP, this binds to the V2-receptor, activating aquaporin channels in the membrane, resulting in high permeability and reabsorption of most water. By this process, small changes in AVP level can have a large effect on the amount of water excreted by the kidneys [106].

In normal physiologic conditions, AVP secretion and consequently urine production expresses a circadian rhythm, resulting in an increased secretion of AVP and a decreased urine production during sleeping hours [33, 107, 108]. The circadian, or peripheral, clock generates this circadian rhythm. This is a molecular genetic feedback mechanism, present in most peripheral organs and cells, which is centrally regulated by the central clock, located in the suprachiasmatic nucleus of the brain [109]. The central clock generates the central circadian rhythm of the body by synchronizing the environment by receiving light cycle signals from the retina. The peripheral clocks are adjusted by neural and hormonal signals and by indirect behavioral controls via feeding and sleep-wake pattern [110]. Genetic defects in the circadian clock system resulted in adjusted rhythms in both urine production and bladder storage function in mice [110]. Similarly, both in nocturia and in enuresis, this circadian rhythm of AVP secretion and the production of urine seems to be disturbed [33, 107], resulting in increased nocturnal urine production.
AVP secretion is not only influenced by diurnal patterns, but also by aging and gender. Changes in water metabolism due to age are multifold: the composition of body fluid decreases and body fat increases, plasma volume lowers, thirst perception lessens, and renal function decreases. This results in a higher susceptibility for mismatches like dehydration or overhydration and hyperosmolality and hypo-osmolality like hyponatremia [106].

In brief, nocturnal polyuria can manifest itself when the circadian pattern of AVP secretion is disturbed. Other causes of nocturnal polyuria can be extreme high evening fluid intake, a defect in AVP action or solute diuresis caused by congestive heart failure, sleep apnea and

renal insufficiency. Nocturnal polyuria often is idiopathic, due to changes according to age [99]. In general, NP causes can be divided in water diuresis and solute diuresis. To distinguish between these two, renal function profiles have recently been proposed to be helpful [111]. Presented like this, nocturnal polyuria presence or absence seems quite straightforward. Unfortunately however, quantifying the presence of nocturnal polyuria is more difficult than it seems, as many different definitions for nocturnal polyuria are available, and the association between nocturnal polyuria and nocturnal voiding frequency was not clear yet.

Definitions of nocturnal polyuria – Pediatric and adult definitions

Both continence societies have published a definition on NP, which are used for enuresis (ICCS) and nocturia (ICS) respectively. The adult, International Continence Society (ICS) definition is: an age-dependent nocturnal urine output exceeding 20-33% of 24-hour urine output; the nocturnal polyuria index [93]. It is therefore a ratio between night-time and 24-hour urine production, in which the first morning void is regarded as night-time urine production. In contrast to the ICS definition, the pediatric continence society, the ICCS, defines nocturnal polyuria as a nocturnal urine production exceeding 130% of the expected bladder capacity for age (EBC), which itself is defined as (age+1)*30 [8, 112]. This definition thus uses the relation between night-time urine production (including the first morning void) and the bladder capacity; a completely different strategy than the ratio of the ICS definition. Alongside these two definitions, more definitions of NP are used in literature, resulting in confusion.

In conclusion, nocturnal polyuria is an important pathophysiologic factor both in nocturia and nocturnal enuresis [8, 32, 100]. A thorough assessment of the conditions is appropriate [89, 99]. For this, insight in the association with nocturnal polyuria and valid definitions for the different causes are needed [89].

Small bladder capacity

Throughout the life span, micturition changes. Neonates show reflex voiding. Postnatally, both enlargement of the bladder capacity and the regulation of the urination by upper central neurons, result in control of both daytime and nighttime micturition [110]. Voided volumes in normal children have a circadian rhythm, the first morning void being larger than all other voidings [113, 114].

Definitions of (small) bladder capacity

The term bladder capacity refers to the amount of urine the bladder is able to store. It can be measured by different means: by cystometry, by cystometry under anesthesia, by the maximum voided volume (MVV) on a Frequency Volume Chart (FVC), or by uroflowmetry [112, 115, 116]. The ICCS defined a small bladder capacity as a bladder capacity lower than 65% of the EBC [8]. For adults, this is unclear, as the most recent ICS report on nocturia terminology states that a definite range of normal or abnormal volumes is lacking and the physician has to evaluate patients based on FVCs and clinical judgment [93]. However, reference values for the general male population have been described: Functional bladder capacity (FBC) was shown to decline with increasing age and lower FBC was related to LUTS [117]. A reduced voided volume can be determined by comparing night-time voided volume with maximal

bladder capacity occurring at any time. Additionally, the ICS document states that the term 'voided volume' replaced the term FBC [93].
Reduced functional bladder capacity is often caused by bladder storage problems, due to BOO, OAB, by neurogenic bladder or by a high PVR, or developmental disturbances [58, 89, 99]. Other causes include LUT cancer, stones and aging [99].

Sleep problems

Both in enuresis and in nocturia, sleep problems are present. In enuresis, these are mainly referred to as arousal problems. In nocturia, it is difficult to distinguish if there is a primary sleep problem that causes people to wake and then to void, or if people awake due to an urge to void, and therefore experience sleep problems.

Children with enuresis are difficult to awake from sleep. For decades, this has been thought to be caused by deep sleep, as questionnaire studies show that enuresis is associated with a subjectively high arousal threshold [118]. Recent research using night-time polysomnography measures however suggests that enuresis patients are merely light, or superficial sleepers. The arousal problems are therefore probably due to several factors. Yeung et al. found that children with severe enuresis (≥5 nights/week) had more light sleep and unstable bladder contractions than non-enuretic children, which was associated with frequent cortical arousals, but no complete awakenings. So, arousal thresholds are increased, probably to maintain sleep time [119]. Respiratory arousal stimuli [120], sleep fragmentation [121], and periodic limb movements during sleep [122] are other factors in play. Additionally, disturbed sleep has a bidirectional relationship with NP; NP can cause sleep deprivation, but sleep deprivation in itself can result in NP as well, by a higher nocturnal blood pressure and lower levels of AVP [123]. The disturbed sleep has an association with behavioral problems. Periodic limb movements were associated with a lower quality of life in 30 MNE patients [122].
So, enuresis can be caused by nocturnal polyuria, bladder problems like detrusor over activity and inadequate arousal mechanisms. This last mechanism can be caused by disturbed sleep, which can be caused by detrusor overactivity, by airway problems (sleep apnea), and has a bidirectional relationship with NP.

Overall, enuresis and nocturia are two conditions with similar etiologies, although many things remain unclear considering definitions and associations of causal factors like nocturnal polyuria and small bladder capacity. Enuresis has mainly been investigated in younger age groups, whereas older patients more often have therapy-resistant enuresis. For this latter group, adapted DBT was developed.

General aims and outline of this thesis

The general aim of this thesis was to study different aspects of enuresis and nocturia, in order to provide a more united view of these two related conditions, focusing on associations with NP, critical

appraisal of current definitions, and evaluating adapted DBT in treatment resistant enuresis patients.

Part I - Nocturia and nocturnal polyuria
This part involves a systematic review and meta-analysis on the association of nocturia and nocturnal polyuria, including a quality assessment of internal and external validity and informativity of included studies. Chapter 2 focuses on the association of nocturia and nocturnal polyuria. It was unclear to what extent NP should be considered the (main) cause of nocturia. Drugs like desmopressin, aiming at reducing nocturnal urine production became newly available in the field of nocturia, to reduce nocturnal voiding frequency. This stresses the importance of assessing the actual association between nocturia and NP in a systematic way. Research questions were as follows: What is the prevalence of NP for people with and without nocturia? What is the nocturnal voiding frequency of people with and without NP? In Chapter 3, the impact of the ICS-2002 report on standardization of terminology in nocturia on publications reporting on nocturia and NP is evaluated in a systematic way. In particular, used nocturia and NP definitions are discussed.

Part II - Enuresis, nocturnal polyuria and functional bladder capacity: focus on definitions
This part focuses on NP and FBC definitions in enuresis instead of in nocturia. The data presented are derived from FVCs and uroflowmetries collected at the initial assessment of adolescent and adult enuresis patients. These patients were treated in a special secondary and tertiary care enuresis center, founded in 2003 by a urologist, a continence nurse and the patient association. In this center, patients suffering from incontinence are assessed. The population studied in this thesis represents a group of 907 therapy-resistant adolescent and adult enuresis patients, treated by adapted Dry Bed Training (DBT) from 2003 to 2013. This training is more extensively described in part III. This part merely focuses on the data of the initial patient assessment, before the adapted DBT. In Chapter 4, the pediatric ICCS and the adult ICS NP definition are compared, as enuresis patients are normally mainly assessed by the ICCS definition, but part of our patients are adults. Additionally, reference values for other FVC and uroflowmetry parameters are presented, as they were lacking for this age group of enuresis patients. Both FVC and uroflowmetry have their advantages and disadvantages, and Chapter 5 focuses on the comparison of these methods to assess FBC.

Part III - Enuresis in adolescents and adults: adapted Dry Bed Training
In this part, adapted DBT for therapy resistant, adolescent and adult enuresis patients is presented. For this, a retrospective cohort study was conducted. Chapter 6 focuses on the description and results of the adapted DBT. Given that these patients have experienced many treatment modalities before, the substantial impact of enuresis and the time-consuming nature of adapted DBT, it is worthwhile to investigate which patients benefit most. Therefore, in Chapter 7, predictors for successful treatment response to adapted DBT in this population are identified. In Chapter 8, long term follow up of adapted DBT is presented. It represents a cross-sectional questionnaire study. Unfortunately, large difficulties regarding response rates were experienced. Therefore, the focus of this chapter is on these problems and on possible solutions.

Finally, in Chapter 9 (Dutch translation in Chapter 10), a summary of this thesis is given, combined with a discussion, recommendations and future research perspectives.

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PART I

Nocturia and nocturnal polyuria

CHAPTER 2

The association between nocturia and nocturnal polyuria in clinical and epidemiological studies: a systematic review and meta-analyses

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Abstract

Purpose

To determine the relationship between nocturia and nocturnal polyuria (NP).

Methods

The Pubmed and Embase databases were searched for studies, written in English, German, French or Dutch, with original data on adult participants, that investigate the relationship between nocturia and NP. A meta-analysis of the difference in mean nocturnal voiding frequencies between patients with and without NP was conducted. Next, NP risk was compared between participants with and without nocturia. The resulting odds ratio (OR) was subsequently converted to relative risk (RR) with 95% confidence interval (CI).

Results

From 511 references identified, we selected 78 publications of 66 studies, 15 of which met the inclusion criteria of this study. Quality scores of studies were generally high for internal validity, but low for external validity. In 7 studies (1,416 participants), we estimated a standardized mean difference of 0.59 (95%CI 0.29-0.89) for nocturnal voidings between NP and non-NP participants. In 8 other studies (with 2,320 participants) we calculated a pooled OR of 4.99 (3.92-6.37) for NP in individuals with nocturia; the corresponding RR, based on a NP risk in the pooled population of 63.8%, was 1.41 (1.37-1.44).

Conclusions

The association between nocturia and NP is apparent and robust. The clinical importance of the association, however, appears to be less obvious than previously suggested based on single studies. The observed high prevalence of NP, as a result of the applied ICS definition, may be responsible for this discrepancy.

Introduction

Nocturia is a common and often bothersome symptom in older men and women, associated with many conditions [1, 2]. One of the potential mechanisms underlying nocturia is that the nocturnal urine production exceeds the nocturnal bladder capacity [3]. Based on this assumption, in 2002 the ICS consensus committee on nocturia, defined nocturnal polyuria (NP) as an age dependent nocturnal urine volume greater than 20% (younger people) to 33% (older people) of 24-hour urine volume (in short Nocturnal Polyuria Index, NPi) [4]. These estimates were based on very low quality evidence [5, 6].

In recent consensus meetings, the ICS definitions were re-evaluated and left unchanged [7]. Two or more nocturnal voidings are considered to be symptomatically bothersome [8]. Recently, Weiss et al. suggested that the majority of patients with nocturia have NP [9]. The cross-sectional nature of the studied population, and the sole inclusion of patients with nocturia, however, preclude a causal inference of this association. Simultaneously, Van Doorn et al. showed that in the general population, the majority of men without nocturia also have NP according to the ICS definition [10]. Earlier, Swithinbank et al. had shown that NP was much more prevalent than nocturia in women [11]. This may be caused by the inclusion of the volume of the first morning void to the nocturnal urinary volume measurement. In patients without nocturia, this morning volume may be large. It might also suggest that NP is not the cause of nocturia, but rather is a concomitant finding. Furthermore, this might suggest that the ICS definition should be re-evaluated. However, it is unclear to what extent NP should be considered as the (main) cause of nocturia.

With the availability of drugs aimed to reduce nocturnal urine production, in order to decrease nocturnal voiding frequency (NVF), we believe it is important to evaluate and review the actual association between nocturia and NP based on study outcomes on this topic, especially when considering the potential side effects in older adults. Therefore, we performed a systematic review and meta-analysis with the main goal to summarize and analyse the pooled association between nocturia and NP. This was evaluated by addressing two research questions. First: what is the prevalence of NP for people with and without nocturia? And secondly: what is the nocturnal voiding frequency of people with and without NP?

Methods

Search strategy

We performed a systematic review of the literature by searching the Pubmed and Embase database without time restrictions. On April 12th 2013, we searched the databases using the terms: Embase: [“nocturnal polyuria” OR [nocturnal AND [“urine production” OR “urine volume”]] NOT child Pubmed: [“nocturnal polyuria” OR [nocturnal AND [“urine production” OR “urine volume”]] NOT children (MeSH Terms). Two authors (IH and MHB) independently screened title and available abstracts. Potential relevant publications were read full text to see if the study included original patient data and associations between nocturia and NP were studied. For feasibility reasons, we

used the following language restrictions: English, German, French, and Dutch. Case reports, reports on specific patient groups (e.g. renal transplantation, diabetes insipidus) and nocturnal enuresis in children, as well as studies in laboratory settings, were excluded.

Selection of studies

Each citation was classified as 'inclusion', 'uncertain', or 'exclusion'. In case of disagreement between the two reviewers, consensus was reached based on discussion. After this, excluded studies were no longer considered. Reference lists of included publications, as well as relevant reviews on this topic, were checked for studies not included in the primary search.

Methodological data assessment

We expected that the majority of studies on this topic would be observational studies. Therefore, we chose to apply a criterion list for the methodological quality assessment, which was used in an earlier systematic review of observational data [12]. This includes three categories: external validity, relating to the applicability of study results to other populations, internal validity, implying accurate measurement apart from random error, and informativity, indicating the presentation of the reports. We tailored this list for this topic by adding criteria on the completeness of data on nocturia and NP, including the definition of night, and use of actual sleeping times (see Appendix A).

Data extraction

Two reviewers (IH, MHB) independently extracted results from the included studies. For feasibility reasons, the quality assessment was not blinded. In case of disagreement, consensus was reached. When no or insufficient information was provided in the article, earlier publications on the same study were used for lacking information, if available. No additional searches were performed and we did not attempt to get in direct contact with authors of published papers. If more than one publication was available from one study, information from those publications was grouped.

Meta-analyses on the association between nocturia and NP

To address the first study question, we selected studies in which NP was compared between participants with and without nocturia, or between participants with various degrees of nocturia. For the second study question, we selected studies in which NVF was compared between participants with and without NP. Studies including only participants with nocturia (without presenting the degree of nocturia) and NP were excluded from the meta-analyses, because no relevant associations can be obtained from such studies.

Meta-analyses were performed with RevMan 5.2 (The Cochrane Library). The percentage of participants with NP was compared between patients with and without nocturia. For this purpose, 2 or more nocturnal voidings were defined as nocturia and less than 2 voidings as no-nocturia. We chose to use this cut-off value for NVF, as this represents a threshold at which nocturia is more likely to be symptomatically bothersome [8]. The pooled odds ratio (OR) was estimated for available studies, using a Mantel-Haenszel Fixed effects model. In this analysis, a significant OR > 1 implies an increased risk for NP in participants with nocturia.

As NP is a prevalent disorder, and interpretation of the pooled OR presents a challenge. ORs are often interpreted as relative risks (RR), but this is only reliable for non-prevalent conditions. Because

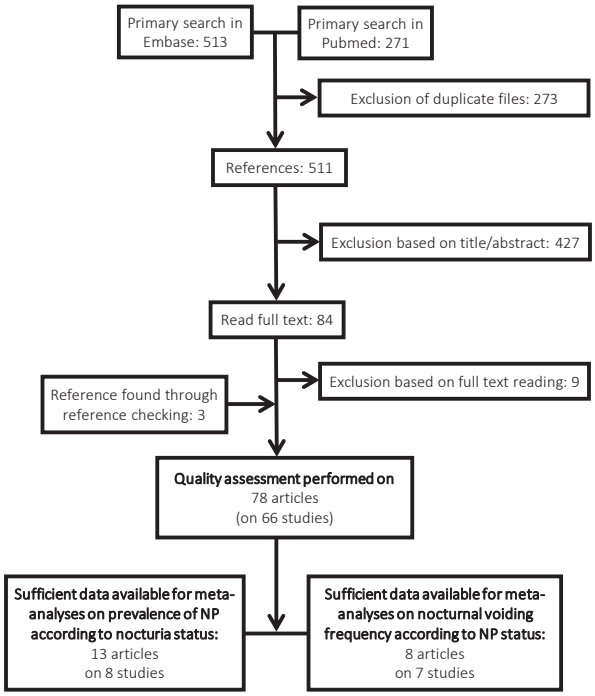

Figure 1. Flow chart of study selection

RRs are better understood by physicians, we converted the OR into RR, using the following formula, in which p presents the risk in the studied population and results from the prevalence of the pooled population: [13]

$$Relative\ Risk = \frac{Odds\ Ratio}{(1-p) + (p * Odds\ Ratio)}$$

For the comparison of the mean NVF between patients with and without NP, we estimated the standardized mean difference, using a random effects model. SMD is presented with 95% confidence intervals (CI95%).

Results

Selection of studies

The search strategy resulted in 78 publications with information about 66 studies on this topic (see Figure 1). To answer our research questions, 15 studies contained sufficient data for meta-analysis. Bibliographic information of these studies is presented in Appendix B.

Methodological quality assessment and description of selected studies

Table 1 shows the quality assessment. On average, 1.73 items (range 0-5) on external validity were scored positive. On internal validity this was 5.4 (range 4-6). Cohen's Kappa coefficient was 0.74.

Study		External validity						Internal validity							Informativity								
number	Year of publication	a[A]	b	c	d	e	Sum	f	g	h	i	j	k	Sum	l	m	n	o	p	q	r	Sum	Disagreement[B]
Studies included in meta-analyses concerning the prevalence of NP in patients with and without nocturia																							
I	2007,2012	+	+	-	-	+	3	+	+	+	+	+	+	6	+	+	+	+	+	+	+	7	a,e,g,o
II	2003	-	-	-	-	-	0	+	+	+	+	+	+	6	+	+	+	+	+	+	+	7	a,b
III	2000, 2002,2012	+	+	+	+	+	5	+	+	+	+[C]	+[D]	+	6	+	+	+	+	+	+	+	7	g,o,p
IV	2003	-	-	-	+	-	1	+	-	+	+	+	-	4	+	+	+	+	+	+	+	7	a
V	2002,2003	-	+	-	-	+	2	+	+	+	+	+[E]	+	6	+	+	+	+	+	+	+	7	a,o,q,r
VI	2004	-	+	?	-	-	1	+	+	+	+	+	+	6	+	+	+	+	+	+	+	7	p
VII	2009, 2010	-	+	?	-	+	2	+	+	+	+	+	+	6	+	+	+	+	+	+	+	7	a,q
VIII	2000	-	-	?	-	-	0	+	+	+	+	+	+	6	+	+	+	+	+	+	+	7	a,p
Studies included in meta-analysis concerning the nocturnal voiding frequency in people with and without NP																							
IX	1999, 2003	-	+	?	-	-	1	+	+	+	+	+	+	6	+	+	+	-	+	+	+	6	a,c
X	2006	-	+	?	-	-	1	+	+	+	+	+	-	5	+	+	+	+	+	+	+	7	a
XI	2006	-	+	?	-	+	2	+	+	+	+	-	-	4	+	+	+	+	-	-	-	4	a,c,o,p,q,r
XII	2007	-	+	+	-	-	2	+	+	+	-	-	+	4	+	+	+	-	+	+	+	6	
XIII	2007	-	-	+	+	-	2	+	+	+	+	+	-	5	+	-	-	+	+	+	-	4	m,n,r
XIV	2012	-	+	+	-	+	3	+	+	+	+	+	-	5	+	+	+	-	+	+	+	6	a,g
XV	2012	-	+	?	-	-	1	+	+	+	+	+	+	6	+	+	+	+	+	+	+	7	n
Sum scores		2	11	4	3	6	1.73	15	14	15	14	13	10	5.4	15	14	14	12	14	14	13	6.4	

Table 1. Quality assessment of included studies. Study numbers refer to Appendix B. Studies are ordered identical to the order used in Figures 2 and 3. A Items a – r refer to Appendix A. B Items on which the two reviewers disagreed; consensus reported. C 3 day FVC with 1 day volume measurement D Fixed time periods for NP, actual sleeping times for nocturia. E Strange definition of night urine volumes: 11 pm- 2 am. For frequency count other definition 11pm-7am. Abbreviations: FVC: Functional Bladder Capacity; NP: Nocturnal Polyuria

Appendix A. Quality score criteria and informativity*

External validity

Selection of the study population

A Clear description of the research population?**

B Inclusion and exclusion criteria described?***

Participants and non-responders

C Response rate > 70% or sufficient information on non-responders?¥

Relationship with source population?

D Extrapolating results possible for the complete population?¥¥

Description of the study period

E Clear description of the study period?

Internal validity

Data collection

F Data prospectively collected?

Measurement instrument

G Measuring instrument for nocturia¥¥¥

H Measuring instrument for nocturnal polyuria∞

I Measuring period: length of FVC or questionnaire presented?

J Definition of night described and actual sleeping times (as reported on FVC) used?

Confounders

K Confounders described?∞∞

Informativity#

L Clear theoretical introduction with relevant references to support the research question?

M Aims of the study clearly described?

N Research questions being answered?

O Definition of nocturia clearly described, or nocturnal frequencies clearly presented (without a cut-off for nocturia)?

P Definition of NP clearly described, or nocturnal urine production, nocturnal voided volumes, or nocturnal polyuria indices clearly presented (without a cut-off for abnormal values)?

Q Clear description of the way data were analysed?

R Enough original data to evaluate their interpretation

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* Items were scored positive if clear information was presented in the articles. Unclear data are presented as "?" and consequently scored negative for the quality score summation.

** Clear description of source and two or more of the following: age distribution, relevant comorbidity, medication

*** Scored positive if both inclusion and exclusion criteria were provided

¥ Sufficient information on non-responders: were reasons for non-response studied and presented, including information on age distribution, gender, main topic under study?

¥¥ Did the study selection procedure result in a representative sample of the study population?

¥¥¥ Data on nocturnal frequency collected through FVC or validated questionnaire

∞ Data on NP or nocturnal voided volumes collected through FVC

∞∞ Description of confounders not necessarily including actual statistical adjustment for confounders.

Informativity was not included in the quality score.

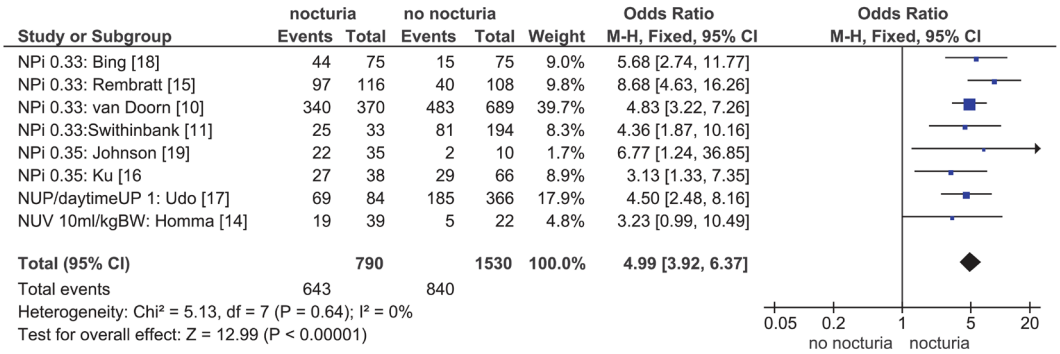

Figure 2. Risk (OR) of nocturnal polyuria according to nocturia status. Pooled Odds Ratio with 95% confidence interval (CI), resulting from meta-analyses using Mantel Haenszel Fixed effects model. Nocturia defined as ≥2 voidings per night. Presentation sorted on applied definition of nocturnal polyuria. NPi: nocturnal polyuria index; NUP: nocturnal urine production; UP: urine production; NUV: nocturnal urine volume; BW: body weight.

For both meta-analyses, we included in total one RCT, three non-randomized trials, two case control studies and nine cross-sectional observational studies totalling 3,736 participants (Table 2). Five studies were community-based, one originated from primary care populations, 4 from secondary and/or tertiary care and in 5 studies the setting of the participants was not clear. In 8 studies, the study period was not reported. In 5 studies, only participants with nocturia were included. Most studies used a frequency volume chart (FVC) for the collection of NVF and voided volumes.

Comparison of NP prevalence between people with and without nocturia

Eight studies with 2,320 participants (1,503 male, 817 female) were available for the comparison of the NP prevalence between people with and without nocturia [10, 11, 14-19]. A funnel plot showed no indication of publication bias. As presented in Figure 2, this equation yielded a pooled OR of 4.99 (3.92-6.37). Estimated RR, based on the NP risk in the studied population of 63.8%, was 1.41 (1.37-1.44). Excluding the largest study from these analyses did not impact the results (5.10 [3.78-6.88]). There was a small difference between the pooled OR of the four studies using the NPi33 definition (5.45 [4.07-7.32]) and the 2 studies using the NPi35% definition (3.71 [1.74-7.90]). Subgroup analyses showed no apparent differences (p=0.72) between the 7 descriptive studies (OR 4.93, 3.81-6.37) and the included case control study (OR 5.68, 2.74-11.77).

Comparison of NVF between people with and without NP

Seven studies totalling 1,416 participants (368 male, 43 female [20-25]; one study with 1,005 male and female participants did not present gender differences [26]) were available for the comparison of NVF between participants with and without NP. Funnel plot analysis showed no indication of publication bias. Pooled analyses generated a standardised mean difference in NVF of 0.59 (95% CI 0.29-0.89). Subgroup analyses showed no significant difference (p=0.28) between the two descriptive studies and three non-randomised trials: SMD, respectively, 1.32 (0.55-2.09) and 0.79 (0.21-1.37).
For both comparisons, the selected studies did not present gender-specific findings, making subgroup analyses based on gender impossible.

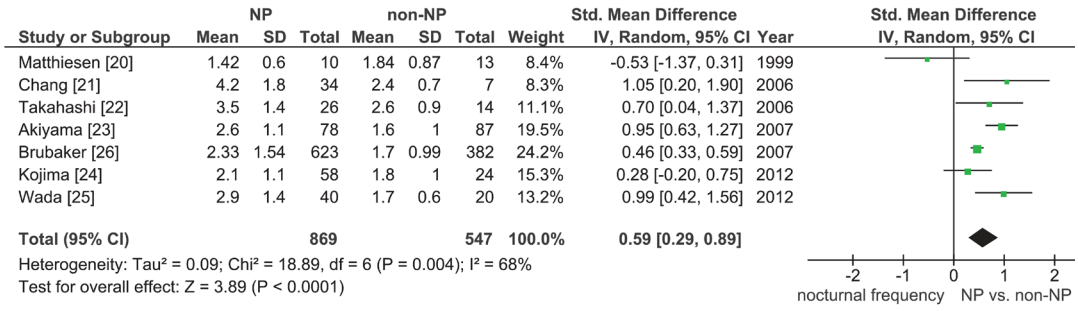

Figure 3. Standardised mean difference in nocturnal voiding frequency between participants with and without nocturnal polyuria (NP). Standardised mean difference with 95% confidence interval (CI) in nocturnal voiding frequency between participants with and without nocturnal polyuria (NP), resulting from meta-analyses using a random effects model. Presentation in order of publication year.

Discussion

In this systematic review and meta-analyses the observed association and difference between nocturia and NP is conclusive: the relative risk for NP was 1.43 for patients with NVF ≥ 2, compared to those with less nocturnal voidings. It appeared, however, that the mean NVF for patients with NP is only 0.59 higher than for those without NP.

To the best of our knowledge, this is the first publication investigating the association between NP and nocturia in a systematic way. Previous reports, including a number of reviews, were limited to single studies, or were non-systematic, lacking quality assessment and critical review of earlier publications [1, 7]. As nocturia is believed to have a multifactorial origin, it should be remembered that there are other possible causes of nocturia, such as reduced bladder capacity and sleep quality. In only a few of the included studies in this review, such factors were considered. The search strategy appeared to be both specific and sensitive. That is, only three studies were not included in the primary search, but were identified based on reference checking. Due to the applied language restrictions, we may not have identified all relevant publications on this subject. In our study, a large number of publications originated from Asian countries. Therefore, we cannot rule out that other available publications were not included in our review.

The external validity of most studies included in our review is considered a problem. This even pertained to the report on the RCT, for which clarity of reporting is crucial. Sufficient information on the background of study population was provided in only two studies. We argue that results of only three studies could be extrapolated to the population at large. Internal validity and informativity scores were generally high. Conspicuously, NP and nocturia were not defined in one and three studies, respectively. In one study, night was undefined and in one fixed sleeping time periods were used. The ICS definition for NP, or definitions with closely approximated cut-off values, was the most often used in the included studies. We were somewhat surprised to notice that in many of the 78 assessed publications, unusual comparisons were made, such as NVF between author-defined groups of people with and without nocturia, and mean urine production or voided volumes between

NP and non-NP participants.

Only 15 studies were available for meta-analyses. This reflects a limitation in available data in publications on this topic. A large number of studies included only participants with nocturia, or only participants with NP. From such studies, no conclusions can be drawn on the possible association between nocturia and NP. It appeared that for both analyses, study results were quite similar. In the comparison of NVF between NP and non-NP, only one out of seven studies showed a lower NVF in NP-participants. All included studies on the comparison of NP-prevalence according to nocturia status showed a clear increased risk for NP in people with nocturia. It should be noticed that included data were based on cross sectional studies. The results of cross-sectional studies do not allow to make any causal inferences. Although non-causal associations may be of clinically importance as well, the reported OR should be interpreted with some caution. Additionally, it should be stressed, that the observed ORs must not be interpreted as a RRs, which is often done in clinical research [13]. Especially, due to the high prevalence of NP in the pooled study population (63.8%), the OR only reflects a relative risk of 1.43.

This small relative risk we observed is in accordance with the small difference in NVF between individuals with and without NP. This shows that the clinical relevance of the association between nocturia and NP is less obvious than previously suggested. We believe that this might reflect a problem with the applied ICS definition of NP. This consensus definition was based on low quality evidence [5, 6]. Although applying this definition results in a majority of nocturia patients being diagnosed with NP [9], it is now clear that the majority of people also meet the criteria for NP. In fact, the prevalence of NP according to the ICS definition is higher than the prevalence of (symptomatically bothersome) nocturia [11]. Therefore, the ICS definition has a very limited discriminative value in patients with nocturia. To date, other NP definitions also lack an evidence base. For future studies and for daily practice, it is important that definitions of diseases or conditions are based on a solid pathophysiological background, but also on thoroughly testing of definitions in different settings.

Both nocturia and NP vary over time [10, 27]. Only recently, Van Doorn et al. presented the longitudinal data on possible risk factors for nocturia from their population-based study [28]. This clearly showed that NP was an important predictor for the presence of nocturia. In their analyses, two definitions of NP were included: i.e. one based on the ICS definition (a ratio between daytime and nocturnal urine production) and one on a cut off value of 90 ml/hr for nocturnal urine production (NUP90) (not considering daytime urine production). Both definitions appeared to be of importance, without showing statistical interaction, possibly reflecting a difference of principle. Although the ORs for both definitions in that publication were comparable, the corresponding RR differed. Due to a relatively low prevalence of NUP90 (17.5%), its corresponding RR is relatively high at 3.2, whereas the RR for the ICS definition is much lower (RR 1.2) as a result of its high baseline prevalence rate of 77.8% [10]. Likewise, the clinical impact of the two definitions differs as well. Still, because no study has yet replicated the analyses performed by Van Doorn et al., it is unclear how this definition performs in other populations, for example in secondary care.

Conclusions

Despite the methodological problems encountered in this review, we conclude that the association between nocturia and NP is apparent and robust. The clinical importance of the association, however, appears to be less obvious than previously suggested based on single studies. The observed high prevalence of NP, as a result of the applied ICS definition, may be responsible for this discrepancy.

Study nr	Year	Country	Type of study	Participants	Origin	Inclusion criteria	Exclusion criteria	No (%)	Study period	Measurement instrument for nocturia	Measurement instrument for NP	FVC length (days)	Applied definitions night	Applied definitions Nocturia	Applied definitions NP
Studies included in meta-analyses concerning the prevalence of NP in patients with and without nocturia															
I	2007 2012	Denmark	Case control	men/women with/without nocturia	CB	respondents in a population study of 4,000 men/women 60 to 80 years old, answering a question on nocturia	night shift work, severe physical disability, or mental impairment (dementia) and inability to follow instructions.	150 / 1111 (13,5%)	January 2003-January 2005	FVC	FVC	3	actual	2 or more voids	NPi 0.33
II	2003	Sweden	Descriptive	men/women with/without nocturia	CB	inhabitants aged ≥65 years in Tierp, a rural community in Sweden	not defined	2866/4264 (67%); 290/517 (56%)/ 224/517 (43%)	?	FVC	FVC	3	actual	2 or more voids	NPi 0.33
III	2000 2002 2012	the Netherlands	Descriptive	men with/without nocturia	CB	community dwelling men living in Krimpen aan den IJssel, the Netherlands, aged 50 to 75 years, filled in FVC	previous transurethral or open prostatectomy, prostate or bladder cancer, neurogenic bladder disease, or negative advice from their primary care physician (PCP) based on poor health (e.g., being bedridden).	1396/1597 = 87%, 1688/3942 (50%)	1995-1997	both FVC and IPSS	FVC	3 day FVC (1-day volume)	fixed for NP - actual for nocturia*	nocturia 2 (2 or more) and nocturia 3 (3 or more)	various definitions (NPi 0.33, NUP>90 ml/h)
IV	2003	UK	Descriptive	women with/without nocturia	PC	age≥50, previously taken part in the prevalence study of LUTS among women registered with one family doctor practice	not defined	264/1183 (19,5%)	?	?	FVC	7	actual	2 or more voids	NPi 0.33
V	2002 2003	USA	Descriptive	men/women with/without nocturia	CB	age ≥ 65	overt and symptomatic congestive heart failure, venous insufficiency with pitting edema, DM with poor control, BOO or incomplete bladder emptying (PVR > 200 ml), anemia or UI more than once daily.	45/190 (24%)	July 1997-September 2000	FVC	FVC	7	Fixed (11 PM- 7 AM, 11 PM- 2 AM for volumes and 11 PM-7 AM for frequency)	2 or more voids	NPi 0.35
VI	2004	Korea	Descriptive	men/women with/without nocturia	?	consecutive patients with LUTS, age≥50, could communicate, understand and comply with the study requirements	confused state or depressed, used medications to control bladder symptoms, pregnancy, UTI (bacteriuria of ≥ 104 bacteria/mL of voided urine), working primarily at night, incomplete evaluation because the charts had missing dates, not consecutive days or only 2 days of data	104/….? (?%)	?	FVC	FVC	3	actual	1 or more, or 2 or more in 3 nights	NPi 0.35 & NBCi

Study nr	Year	Country	Type of study	Participants	Origin	Inclusion criteria	Exclusion criteria	No (%)	Study period	Measurement instrument for nocturia	Measurement instrument for NP	FVC length (days)	Applied definitions night	Applied definitions Nocturia	Applied definitions NP
VII	2009 2010	Japan	Descriptive	men/women with/without nocturia	CB	community-dwelling people who underwent a mass screening program in a rural town in Hokkaido, Japan, and 75 outpatients who consulted the Department of Urology, Meiji University of Integrative Medicine, with various complaints including nocturia	24-hour polyuria (>40mL/ kg), suspected of suffering from definite pathological disorders such as cancer of the bladder, bladder stone, bacterial cystitis, cancer of the prostate and prostatitis, no completed bladder diary, no consent to participation in the study	450/ 694	April 2005 - December 2006	FVC	FVC	3	actual	mild: 1, severe 2 or more. Ref 142: 1 or more	Proportion NUP rate (ml/ min) / datyime UP rate > 1 , NPi 0.33
VIII	2000	Japan	Descriptive	men/women with/without nocturia	SC	All: hospitalized patients. (asymptomatic population:) apparently healthy and subjectively free of LUTS, no evidence of disorders affecting LUT function. (elderly population complaining of nocturia) nocturia, apparently healthy and free of disorders affecting LUT function	study 1: Qmax <10 ml/sec, PVR>30 ml study 2: not defined	67 + 39 / ??	?	FVC	FVC	1	actual	2 or more voids	NUV/body weight >10 ml/kg
Studies included in meta-analysis concerning the nocturnal voiding frequency in people with and without NP															
IX	1999 2003	Denmark	Case control	men with/without nocturia	SC/TC	patients: consecutively referred to department with LUTS for BPH evaluation & age matched controls with no history of nocturia or any other urological complaints	All: abnormalities on physical examination, history of renal, cardiac or hepatic disease, abnormal clinical blood pressure, bacteriuria, proteinuria and glucosuria. Controls: Qmax < 14 mL/s	11 + 23 / ??	?	FVC	FVC	7	actual	not defined	NUP > 2 SD of the mean (of the controls)
X	2006	Taiwan	Descriptive	men with nocturia	?	patients: nocturia. Controls: asymptomatic young men	history of CVA, congestive heart failure, liver disease with ascites, COPD, chronic renal insufficiency, malignancy of the genitourinary system, polydipsia, or psychogenic insomnia.	41 / ?	?	FVC	FVC	3	actual	2 or more voids	NPi 0.35

Study nr	Year	Country	Type of study	Participants	Origin	Inclusion criteria	Exclusion criteria	No (%)	Study period	Measurement instrument for nocturia	NP	FVC length (days)	Applied definitions night	Nocturia	NP
XI	2006	Japan	Non-randomised	men with nocturia	SC/ TC	≥1 urinary urgency/day, IPSS≥8, ≥3 in any of the scores for three items (frequency, nocturia, and urgency) of IPSS	suspicion of prostate cancer based on DRE and PSA, any complications possibly affecting voiding function (neurogenic bladder, urethral stricture, active UTI and cerebrovascular diseases); any history of BPH treatment and concomitant medication (other α1-blockers, antimuscarinic agents)	82 / ?	June 2000 - December 2003	FVC	FVC	2	not defined	1 or more voids	not defined
XII	2007	?	Descriptive	men with nocturia	?	age≥ 50, nocturia	past or present heart disease, DM with a fasting blood glucose of 200 mg/dL or more, serum Cr greater than 1.5 ng/dL, hydronephrosis, PVR≥50 ml, urinary incontinence influencing exact measurement of urine volume, UTI, habitual use of diuretics, lithium, 24-h production ≥40 mL/kg body weight	165/189 = 87%	?	FVC	FVC	?	Fixed (10 PM – 6 AM)	not defined	NPi 0.35 and NUV > 0,9mL/ min* sleeping hours
XIII	2007	USA	RCT	men/women with nocturia	?	age≥ 18, mean ≥8 voids/24h, ≥1 urgency episodes/24h	not defined	2534/ 3032 (83,6%)	?	FVC	FVC	3	actual	1 or more voids	NUV> (hrs of sleep / 24 hr)*24hr
XIV	2012	Japan	Non-randomised	men with/without nocturia	TC	BPH, IPSS >7, Qmax <15 ml/ sec, prostate volume>20 ml	neuropathic disorders including DM or UTI	82/115 (71%)	2002-2008	both FVC and IPSS	FVC	3	actual	not defined	NPi 0.33
XV	2012	Japan	Non-randomised	men/women with nocturia	?	OAB, nocturia	urinary tract malignancy, PVR >100 ml, bladder stone, UTI, severe heart disease, liver dysfunction, renal dysfunction, dementia. Concomitant treatment with other medications that would affect LUT function, including other anticholinergic drugs, a-adrenergic antagonists, medications for Parkinson disease and depression, and antihistaminergic drugs.	60/...?	?	FVC	FVC	2	actual	2 or more voids	NPi 0.33

Table 2. Characteristics of studies included in meta-anlysis. Study numbers refer to Appendix B. Studies are ordered identical to the order used in Figures 2 and 3. Abbreviations: BOO: bladder outlet obstruction; BPH: benign prostate hyperplasia; CB: community based; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; DM: diabetes mellitus; DRE: digital rectal examination; FVC: frequency volume chart; LUT: lower urinary tract; LUTS: lower urinary tract symptoms; NBCi: Nocturnal Bladder Capacity index; NP: nocturnal polyuria; NUV: nocturnal urine volume; NUP: nocturnal urine production; OAB: overactive bladder; PC: primary care; PVR: post void residual volume; Qmax: maximal urinary flow rate; RCT: randomized controlled trial; SC: secondary care; TC: tertiary care; UTI: urinary tract infection

Appendix B. Bibliographic information on studies included in the meta-analysis.

Study	References included
Prevalence of NP in patients with and without nocturia	
I	Bing, M. H., Moller, L. A., Jennum, P. et al.: Pathophysiological Aspects of Nocturia in a Danish Population of Men and Women Age 60 to 80 Years. J Urol, 178: 552, 2007
	Bing, M. H., Jennum, P., Moller, L. A. et al.: Obstructive sleep apnea in a danish population of men and women aged 60-80 years with nocturia. J Clin Sleep Med, 8: 515, 2012
II	Rembratt, A., Norgaard, J. P., Andersson, K. E.: Differences between nocturics and non-nocturics in voiding patterns: An analysis of frequency-volume charts from community-dwelling elderly. BJU Int, Suppl, 91: 45, 2003
III	Blanker, M. H., Bohnen, A. M., Groeneveld, F. P. et al.: Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol, 164: 1201, 2000
	Blanker, M. H., Bernsen, R. M. D., Bosch, J. L. H. R. et al.: Relation between nocturnal voiding frequency and nocturnal urine production in older men: A population-based study. Urology, 60: 612, 2002
IV	Van Doorn, B., Blanker, M. H., Kok, E. T. et al.: Prevalence, incidence, and resolution of nocturnal polyuria in a longitudinal community-based study in older men: The Krimpen study. Eur Urol, 63: 542, 2013
	Swithinbank, L. V., Vestey, S., Abrams, P.: Nocturnal polyuria in community-dwelling women. BJU Int, 93: 523, 2003
V	Johnson, T. M., Sands, J. M., Ouslander, J. G.: A prospective evaluation of the glomerular filtration rate in older adults with frequent nighttime urination. J Urol, 167: 146, 2002
	Johnson, T. M., 2nd, Miller, M., Pillion, D. J. et al.: Arginine vasopressin and nocturnal polyuria in older adults with frequent nighttime voiding. J Urol, 170: 480, 2003
VI	Ku, J. H., Lim, D. J., Byun, S. S. et al.: Nocturia in patients with lower urinary tract symptoms: Association with diurnal voiding patterns. BJU Int, 93: 1005, 2004
VII	Udo, Y., Nakao, M., Honjo, H. et al.: Sleep duration is an independent factor in nocturia: Analysis of bladder diaries. BJU Int, 104: 75, 2009
	Udo, Y., Nakao, M., Honjo, H. et al.: Analysis of nocturia with 24-h urine volume, nocturnal urine volume, nocturnal bladder capacity and length of sleep duration: Concept for effective treatment modality. BJU Int, 107: 791, 2010
VIII	Homma, Y., Yamaguchi, O., Kageyama, S. et al.: Nocturia in the adult: Classification on the basis of largest voided volume and nocturnal urine production. J Urol, 163: 777, 2000
Nocturnal voiding frequency in people with and without NP	
IX	Matthiesen, T. B., Rittig, S., Mortensen, J. T. et al.: Nocturia and polyuria in men referred with lower urinary tract symptoms, assessed using a 7-day frequency-volume chart. BJU Int, 83: 1017, 1999
	Matthiesen, T. B., Rittig, S., Djurhuus, J. C.: Functional bladder capacity and urodynamics in males with nocturia. APMIS. Suppl: 59, 2003
X	Chang, S. C., Lin, A. T. L., Chen, K. K. et al.: Multifactorial nature of male nocturia. Urology, 67: 541, 2006
XI	Takahashi, S., Tajima, A., Matsushima, H. et al.: Clinical efficacy of an (alpha)1A/D-adrenoceptor blocker (naftopidil) on overactive bladder symptoms in patients with benign prostatic hyperplasia. Int J Urol, 13: 15, 2006
XII	Akiyama, T., Hirayama, A., Fujimoto, K. et al.: Cutoff Value of Urinary Arginine Vasopressin for Nocturnal Polyuria in Elderly Men. Urology, 69: 98, 2007
XIII	Brubaker, L., FitzGerald, M. P.: Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. Int Urogynecol J Pel, 18: 737, 2007
XIV	Kojima, Y., Sasaki, S., Imura, M. et al.: Tamsulosin reduces nighttime urine production in benign prostatic hyperplasia patients with nocturnal polyuria: A prospective open-label long-term study using frequency-volume chart. Neurourol Urodyn, 31: 80, 2012
XV	Wada, N., Watanabe, M., Kita, M. et al.: Effect of Imidafenacin on Nocturia and Sleep Disorder in Patients with Overactive Bladder. Urol Int, 89: 215, 2012

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16. Ku JH, Lim DJ, Byun SS, Paick JS, Oh SJ. Nocturia in patients with lower urinary tract symptoms: Association with diurnal voiding patterns. BJU Int. 2004;93:1005-8.
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CHAPTER 3

Impact of the International Continence Society report on the standardisation of terminology in nocturia on the quality of reports on nocturia and nocturnal polyuria: a systematic review

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Abstract

Introduction

To systematically review and evaluate the impact of the ICS-2002 report on standardisation of terminology in nocturia, on publications reporting on nocturia and NP. In 2002, the International Continence Society (ICS) defined nocturnal polyuria (NP) as a NP index (nocturnal urine volume/total 24-h urine volume) exceeding 0.2-0.33, depending on age.

Methods

In April 2013 the Pubmed and Embase databases were searched for studies (in English, German, French or Dutch) based on original data and adult participants, investigating the relationship between nocturia and NP. A methodological quality assessment was performed, including scores on external validity, internal validity and informativity. Quality scores of items were compared between studies published before and after the ICS-2002 report.

Results

The search yielded 78 publications based on 66 studies. Quality scores of studies were generally high for internal validity (median 5, IQR 4-6) but low for external validity. Following publication of the ICS-2002 report, external validity showed a significant change from 1 (IQR 1-2) to 2 (1-2.5, p=0.019). Nocturia remained undefined in 12 studies. Nineteen different definitions were used for NP, most often being the ICS (or similar) definition: this covered 52% (n=11) of studies before and 66% (n=27) after the ICS-2002 report. Clear definitions of both nocturia and NP were identified in 67% and 76% before, and in 88% and 88% of the studies, respectively, after the ICS-2002 report.

Conclusions

The ICS-2002 report on standardisation of terminology in nocturia appears to have had a beneficial impact on reporting definitions of nocturia and NP, enabling better interpretation of results and comparisons between research projects. Because the external validity of most of the 66 studies is considered a problem, the results of these studies may not be validly extrapolated to other populations. The ICS definition of NP is used most often. However, its discriminative value seems limited due to the estimated difference of 0.6 nocturnal voidings between individuals with and without NP. Refinement of current definitions based on robust research is required. Based on pathophysiological reasoning, we argue that it may be more appropriate to define NP based on nocturnal urine production or nocturnal voided volumes, rather than on a diurnal urine production pattern.

Introduction

Nocturia is a common and often bothersome symptom in older men and women. It is associated with many conditions, including depression and obstructive sleep apnoea [1-3], and it is widely acknowledged that nocturia has multiple aetiologies. Nocturnal polyuria (NP) is often considered to be an important cause of nocturia, especially when the nocturnal urine volume exceeds the nocturnal bladder capacity [4]. In the 2002 consensus document on nocturia, the International Continence Society (ICS) subcommittee on the standardisation of terminology in nocturia (hereafter referred to as the ICS-2002 report) provided relevant definitions on this topic. As such, NP was defined as an age-dependent nocturnal urine volume ≥ 20% of 24-h urine volume in younger people, and up to 33% in older people (in short: the Nocturnal Polyuria Index, NPi) [5]. However, this definition was based on limited evidence [6, 7].
In addition to the ICS definition of nocturia (i.e. awakening at night to void), two or more nocturnal voidings are increasingly considered to be the threshold at which nocturia is more likely to be symptomatically bothersome [8].

Until recently, it was unclear to what extent NP should be considered as the (main) cause of nocturia. To clarify this issue we published a systematic review and meta-analyses [9]. This latter study reported a relative risk of NP of 1.4 for people with two or more nocturnal voidings compared to those with less nocturnal voidings, based on the ICS definition of NP or closely related definitions (NPi 0.30, 0.35). The mean nocturnal voiding frequency of people with NP was 0.6 higher than in individuals without NP [9]. In most patients this small difference may not be considered clinically relevant, although no threshold value exists for improvement in nocturia.
The current systematic review examines the completeness of reports on nocturia and NP. In particular, we aimed to evaluate the impact of the ICS-2002 report on the applied definitions for nocturia and NP in relevant publications.

Methods

The design of the systematic review and meta-analyses has been published in detail elsewhere [9]. On April 12th 2013 the Embase and Pubmed databases were searched using the terms: ["nocturnal polyuria" OR [nocturnal AND ["urine production" OR "urine volume"]].

Two authors (IH and MHB) independently screened the title and available abstracts of relevant studies (published in English, German, French, or Dutch). Then, the full text of potentially relevant publications was read to establish whether the study included original patient data and whether associations between nocturia and NP were investigated. Excluded were case reports, reports on nocturnal enuresis in children or specific patient groups (e.g. renal transplantation, or diabetes insipidus), as well as studies performed in a laboratory setting.

We classified each citation as 'inclusion', 'uncertain', or 'exclusion'. In case of disagreement between the two reviewers, consensus was reached based on discussion. After this, excluded studies were no

longer considered. Reference lists of the included publications, as well as relevant reviews on this topic, were checked for studies not included in the primary search. Publications before and after publication of the ICS-2002 report on the standardisation of terminology in nocturia were included.

Methodological data assessment

As most studies on this topic were expected to be observational studies, we chose to apply the criterion list for the methodological quality assessment used in an earlier systematic review of observational data [10]. This includes three categories: *external validity*, related to the applicability of the study results to other populations, *internal validity*, implying accurate measurement apart from random error, and *informativity*, dealing with the presentation of the reports. For the present study, we tailored this list by adding criteria on the completeness of data on nocturia and NP, including the definition of 'night', and use of actual sleeping hours (Table 2).

Data extraction

Two reviewers (IH, MHB) independently extracted results from the included studies**.** If required, earlier publications on the same study were consulted to substitute/complete missing information. No additional searches were performed and no attempts made to contact the authors of the included publications. If more than one publication was available based on the same study, information from those publications was grouped.

Comparison of studies according to ICS definitions

To study the possible impact of the ICS-2002 report, completeness of publications (assessed by the above-mentioned quality scores) was compared between studies published before and after March 2002. For this, we used the reported date of data collection, date of first submission or acceptation, or date of publication. For the latter, a two-year period was subtracted, reflecting an estimated average time delay between data collection and publication.

In those studies in which data collection started in 2002 but the month was not specified, it is unclear whether data collection took place before or after publication of the ICS-2002 report. Therefore, these studies were excluded from the present 'study'.

Statistical analysis

As quality scores were not normally distributed, these scores are presented as median scores with interquartile ranges (IQR). Differences in internal and external validity scores of studies before and after the ICS-2002 report were tested using the Mann-Whitney U-test. Subgroup analyses were performed for the different study designs. Additionally, for both publication eras (i.e. pre- and post ICS-2002 report), we compared the quality scores between different study types, expecting higher scores for drug trials. For this analysis we grouped randomised controlled trials (RCT) and non-randomised trials (such as open label studies) on the one hand, and case control studies and descriptive studies on the other. For the sub-items of the quality scores, numbers are presented representing the amount of studies that scored positive. Fisher's exact test was used to test the differences before and after the ICS-2002 report for the most relevant sub-items (i.e. the definition of nocturia and NP). Reported p-values are two-sided and a p-value of <0.05 was considered statistically significant. Level of agreement (percentage) was calculated to denote the inter-observer agreement. Statistical

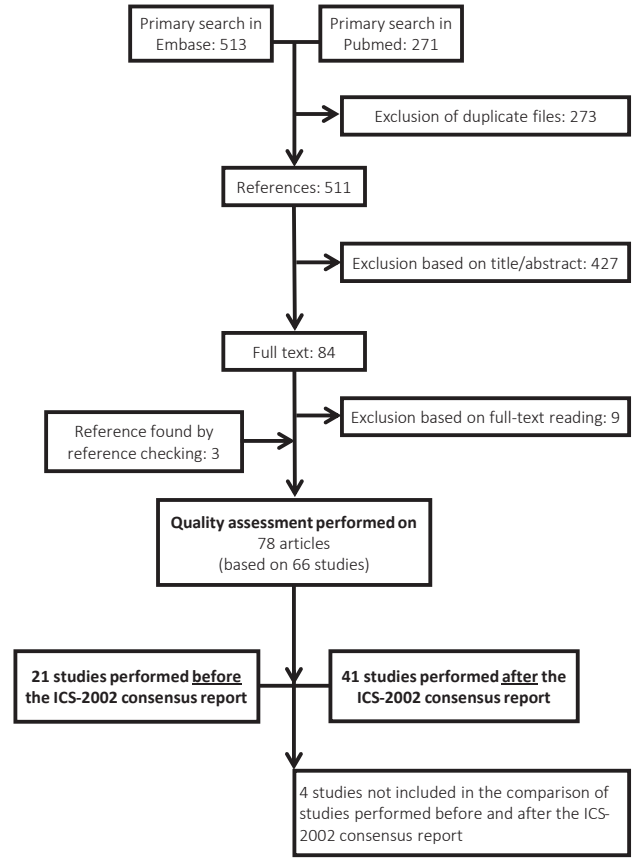

Figure 1. Flow chart of study selection.
(ICS: International Continence Society)

analyses were performed using IBM SPSS Statistics 20.

Results

Selection and description of studies

The search strategy resulted in 78 publications with information on 66 studies, including 3 studies found by reference checking (Figure 1). Bibliographic information of these studies is presented in Appendix A. All these studies were published in the English language. Of the 66 studies, 21 were published before and 41 after the ICS-2002 report; note that 4 of the 66 studies were excluded from the analysis of differences between pre- and post ICS publications. We included 16 RCTs (5 before and 10 after the ICS-2002 report, 1 excluded from ICS analysis); 19 non-randomized trials (4 vs. 15), 5 case control studies (2 vs. 3), and 26 cross-sectional observational studies (10 vs. 13, 3 were excluded).

Study characteristics are presented in Table 1. A total of 20,291 participants were included, the majority of which originated from secondary or tertiary care populations. In 40 studies, [8 (38% of all

		Total	Before ICS-2002	After ICS-2002	
		n (%)	n (%)	n (%)	p-value
		66	21	41	
External validity					
Selection of the study population					
A	Clear description of the research population?**	5 (8)	1 (5)	4 (10)	
B	Inclusion and exclusion criteria described?***	54 (82)	16 (76)	34 (83)	
Participants and non-responders					
C	Response rate >70% or sufficient information on non-responders?¥	16 (24)	3 (14)	12 (29)	
Relationship with source population?					
D	Extrapolating results possible for the entire population?¥¥	7 (11)	2 (10)	5 (12)	
Description of the study period					
E	Clear description of the study period?	29 (44)	7 (33)	21 (51)	
Total external validity score: med [interquartile range]		2 [1-2]	1 [1-2]	2 [1-2.5]	0.019
Internal validity					
Data collection					
F	Data prospectively collected?	63 (95)	20 (95)	39 (95)	
Measurement instrument					
G	Measuring instrument for nocturia¥¥¥	58 (88)	17 (81)	37 (90)	
H	Measuring instrument for nocturnal polyuria∞	58 (88)	17 (81)	37 (90)	
I	Measuring period: length of FVC or questionnaire presented?	54 (82)	15 (71)	35 (85)	
J	Definition of night described and actual sleeping times (as reported on FVC) used?	43 (65)	13 (62)	26 (63)	
Confounders					
K	Confounders described?∞∞	36 (55)	14 (67)	20 (49)	
Total internal validity score: med [interquartile range]		5 [4-6]	5 [3-6]	5 [4-6]	0.944
Informativity					
L	Clear theoretical introduction with relevant references to support the research question?	63 (95)	19 (90)	40 (98)	
M	Aims of the study clearly described?	60 (91)	19 (90)	37 (90)	
N	Research questions adequately answered?	60 (91)	19 (90)	37 (90)	
O	Definition of nocturia clearly described, or nocturnal frequencies clearly presented (without a cut-off for nocturia)?	54 (82)	14 (67)	36 (88)	0.086
P	Definition of NP clearly described, or nocturnal urine production, nocturnal voided volumes, or NP indices clearly presented (without a cut-off for abnormal values)?	56 (85)	16 (76)	36 (88)	0.285
Q	Clear description of the way data were analysed?	57 (86)	17 (81)	36 (88)	
R	Enough original data to evaluate their interpretation	51 (77)	14 (67)	33 (80)	
Total informativity score: med [interquartile range]		7 [5.75-7]	7 [4-7]	7 [6-7]	0.389

Table 2. Comparison of quality score items for studies published before and after the ICS-2002 report**.**
P-values for the overall scores were computed by the Mann-Whitney U-test, for sub-score O and P by Fisher's exact test.
FVC: frequency-volume chart, IQR: interquartile range, ICS: International Continence Society ; Med: median, NP: nocturnal polyuria.
* Items were scored positive if clear information was presented in the articles. Unclear data are presented as "?" and consequently scored negative for the quality score summation.
** Clear description of source and two or more of the following: age distribution, relevant comorbidity, medication
*** Scored positive if both inclusion and exclusion criteria were provided
¥ Sufficient information on non-responders: were reasons for non-response studied and presented, including information on age distribution, gender, main topic under study?
¥¥ Did the study selection procedure result in a representative sample of the study population?
¥¥¥ Data on nocturnal frequency collected through FVC or validated questionnaire
∞ Data on NP or nocturnal voided volumes collected through FVC
∞∞ Description of confounders not necessarily including actual statistical adjustment for confounders.

studies before the ICS-2002 report) vs. 30 (78% of all studies after the ICS-2002 report], participants with nocturia were included but no participants without nocturia.

Internal/external validity and informativity scores

Table 2 shows the quality assessment scores for all studies, categorised according to the two publication eras (i.e. before and after the ICS-2002 report). Agreement between the two observers was 86% for all quality items. For all 66 included studies the median score for external validity was 2 (IQR 1-2); the internal validity score was 5 (4-6), and the informativity score was 7 (5.75-7).

After the ICS-2002 report, the external validity score showed a significant change for all the studies, whereas the internal validity and informativity scores showed no significant change (Table 2). No differences between study types were apparent for the two publication eras (Table 3), and there was no change over time for the separate study types. However, for internal validity scores there was a distinct difference between the drug studies and non-drug studies, with higher scores for the latter before the ICS-2002 report. After the ICS-2002 report, these differences were absent, mostly due to an increase in quality scores for the RCTs (Table 3). For the total group of studies, the change over time was not significant (Table 2).

Completeness of data

In 57 studies, the setting or background of the study population was unclear: 20 (95% of all studies before the ICS-2002 report) vs. 37 (90% of all studies after the ICS-2002 report). In 37 studies the study period was not reported: 14 (67%) vs. 20 (49%). Most studies used a frequency-volume chart (FVC) for both the collection of nocturnal voiding frequency and for voided volumes. In 11 reports the method of data collection was unclear: 4 (19%) vs. 3 (7%), whereas in 5 studies nocturia questionnaires were used: 1 (5%) vs. 4 (10%). In 17 studies, the definition of 'night' was unclear. In

	Before ICS-2002	Difference*	After ICS-2002	Difference*	Difference before and after ICS-2002*
External validity score					
RCT	1 (1-1.5)		2 (1-3)		0.165
Non-RCT	1 (1-1.75)		2 (2-2)		0.124
		0.754		0.778	
Descriptive study	1.5 (0.75-2)		2 (1-2.5)		0.738
Case control study	1 (1-1)		3 (1-..)		0.400
Internal validity score					
RCT	3 (3-4.5)		5 (4-5)		0.055
Non-RCT	4.5 (1.75-5.75)		5 (3-5)		0.736
		0.034		0.181	
Descriptive study	6 (4.75-6)		5 (4-6)		0.232
Case control study	4 (2-..)		6 (6-6)		0.400
Informativity score					
RCT	7 (4-7)		7 (6.75-7)		0.513
Non-RCT	5 (4-6.75)		6 (5-7)		0.307
		0.702		0.453	
Descriptive study	7 (4.75-7)		6 (6-7)		0.483
Case control study	4.5 (3-..)		7 (5-..)		0.400

Table 3. Comparison of quality scores before and after the ICS-2002 report for the different study types. Expressed in medians and interquartile range
*p-values for the Mann-Whitney U test, for comparisons between study types within pre- or post-ICS era, or comparison of study type scores between the two eras. ICS: International Continence Society, RCT: randomised controlled trial

	Nr. of studies
Nocturnal polyuria index (NPi)	
NPi > 0.2 (if < 60 years) or > 0.3 (if > 60 years)	1
NPi > 0.30	1
NPi > 0.33	26
NPi > 0.35	14
NPi > 0.53	1
NPi without cut-off	4
modified NPi > 0.33, based on 8 hr of sleep	2
Nocturnal urine volume (NUV) definitions	
NUV > 0.9 ml/min	2
NUV > 0.9 ml/min * sleep duration	1
NUV > (sleeping hours / 24 h)*24 h	1
NUV / total volume > sleeping hours/24 h	1
NUV > 10 ml/kg body weight	2
NUV > 6.4 ml/kg	1
Nocturnal urine production (NUP) definitions	
NUP > 2 standard deviations of the mean (of the controls)	1
NUP > 90 ml/h	1
Nocturia index (Ni; NUV/maximum voided volume)	
Ni > 1	2
Ni > 1.5	1
Other	
"Passing large amounts of urine at night"	1
Nocturnal Bladder Capacity index	2
Proportion NUP rate (ml/min)/daytime UP rate > 1	1
NP not defined	9

Table 4. Various definitions used for nocturnal polyuria in the 66 included studies. Several studies used more than one definition for nocturnal polyuria. Therefore, these numbers total to more than 66 (the number of studies included).

41 studies, actual sleeping hours were used. The duration of the FVC was undefined in 8 studies.

Applied definitions of nocturia and NP

The following nocturnal voiding frequencies were used to define nocturia: ≥ 1 nocturnal voidings (16 studies), ≥ 2 (34 studies), ≥ 3 (7 studies), and ≥ 4 nocturnal voidings (1 study). However, several studies used more than one definition (Table 1). In 12 studies, nocturia remained undefined: 7 (33%) vs. 5 (12%). Nineteen different definitions for NP were used (Table 4); again, several studies used more than one definition. Most often (n=41) the ICS definition for older people (i.e. NPi >0.33) or definitions similar to that (0.30, 0.35) were used; this covered 52% (11) and 66% (27) of the included studies, before and after the ICS-2002 report, respectively.

Reporting of clear definitions of both nocturia and NP increased after publication of the ICS-2002 report; however, this increase was not significant, 67% vs. 88% (Fisher's exact test p=0.086) and 76% vs. 88 (p=0.285), respectively.

Discussion

This systematic review shows that the quality of reports on nocturia and NP increased after publication of the ICS-2002 report. This document may have been instrumental in encouraging researchers to be clearer about the applied definitions and data collection. This is similar to the study of Cartwright and Cardozo showing that the 2002 ICS standardisation report on lower urinary tract terminology resulted in a significant change in the usage of this terminology [11].

Nevertheless, we encountered several problems that still need attention. For example, in most studies the external validity is considered a major problem. Low external validity impairs the ability to extrapolate the results to the general population. In our opinion, the results of only 7 of the 66 studies might be extrapolated to the population at large; for example, sufficient information on the background of the study population was provided in only 4 studies.

In contrast to the low external validity scores, the internal validity scores were generally high. This implies that measurements in the selected studies were accurate, apart from random error. However, even with these high scores, some essential points were lacking. For example, in 17 studies, 'night' was not defined, or fixed sleeping time periods were used; this even included RCTs for which unambiguous reporting is crucial, as they are often used to make treatment choices. Additionally, NP and nocturia were not defined in 9 and 12 studies, respectively. With a variety of definitions available and being applied, it is important to know which definition is used in each study to enable meaningful comparison between studies. Overall, the majority of studies used a FVC, which is considered the gold standard for collecting information on various measures like urinary production and frequency; this is in line with the ICS recommendations. However, the duration (measurement period) of the FVC needs to be sufficient and clear; this was not the case in all studies.

Effects of the ICS-2002 report on standardisation of terminology in nocturia
After the ICS-2002 report the external validity scores showed a (significant) 1-point increase (on a 5-point scale). We observed an increase of the 25th percentile of 1 and 2 points for, respectively, internal validity (on a 6-point scale) and informativity (on a 7-point scale).

From our data no causal association can be shown between publication of the ICS-2002 report and the change of quality scores. In the ICS-2002 report, although no specific guidelines for reporting are provided, definitions with background information were given. For the majority of the studies, the ICS definition for NP for older people, or closely related definitions, were used. Before the publication of the consensus statement this covered 52% of the included studies compared with 66% after this publication. Moreover, after the ICS-2002 report various other definitions were also used. The various definitions can be grouped according to the concept on which they are based (Table 4). Notably, none of these definitions have been sufficiently validated in different populations.

Nocturnal polyuria index
The nocturnal polyuria index (NPi), as proposed by the ICS, reflects a ratio between night time

urine production and the 24-h voided volume. This definition was based on a small number of low-quality studies, including small groups of patients: i.e. 9 enuretics and 9 healthy controls [6], and 24 young and 21 elderly patients [7]. This definition reflects alterations in the diurnal pattern, which is apparent in men aged ≤ 65 years but not in older men [12].

Based on the ICS definition, NP was present in most patients with nocturia participating in drug trials [13]. On the other hand, the majority of both community-dwelling men and women without nocturia also have NP [14], [15]. Van Haarst and Bosch challenged the ICS definition by proposing a different cut-off value for the NPi, based on a study with healthy volunteers [16]. In that study, the NPi was normally distributed and showed a wide variation. They proposed the upper limit of the 95% confidence interval (CI), being 0.53, to be the cut-off value for NP [16]. Although this intuitively seems a sensible way to express a definition, this results in only a very small proportion of the population having a deviating symptom. In various other conditions (e.g. obesity and hypertension), definitions differentiate in clinically-relevant deviations instead of 95% CIs of the general population [17, 18].

Our earlier meta-analyses showed that people with NP according to the ICS definition experience 0.6 more voids at night than individuals without NP [9]. Hence, the ICS definition probably has a limited added and clinical value. A possible explanation for this is that the first morning void is included in the night-time urine production estimation, but not in the nocturnal voiding count. Hence, people with a large first morning void, who do not get up at night, can easily be categorised as having NP without having nocturia.

To evaluate the actual clinical value of the additional 0.6 nocturnal voidings that people with NP experience according to the ICS definition, more studies are needed to assess the quality of sleep patterns. Only 8 of the 66 studies investigated the number of hours of undisturbed sleep (HUS). If waking 0.6 times less often would result in more HUS and/or initial slow wave sleep, this could have had an impact on well-being and daytime alertness [19]. Possibly, this together with the actual number of nocturnal voids could be responsible for the observed difference between the healthy – or non-bothersome symptom – population and the group of patients with bothersome symptoms of nocturia. If nocturnal voidings are present, but sleep is not considerably disturbed, patients may not necessarily seek medical advice.

Nocturnal urine volume and nocturnal urine production definitions

Ten of the studies used a definition based on night-time assessments only. In this way, inclusion of the first morning voided volume in night-time estimations results in the same problems as for the NPi calculations. Some of the used definitions take the amount of sleeping hours into account. The reference value of nocturnal urine volume > 0.9 ml/min was based on a study in young men (aged 25-35 years) [7, 20]. We believe that these healthy young subjects cannot serve as a reference for older people, because of the diurnal variation of urine production with ageing [12]. The reference value of nocturnal urine production >90 ml/h is based on the Krimpen study, in which 1,432 FVCs from men aged 50-78 years from the general Dutch population were collected at baseline. The nocturnal urine production was estimated as the mean hourly urine production from 1

AM to 6 AM, in which 90% of the men were asleep [21]. The cut-off value resulted from multivariable logistic regression analyses in which various cut-off values were entered. The model including the 90 ml/h value was determined to be the best model, based on the highest percentage of explained variance. However, even this best cut-off value appeared to have only modest discriminative value in cross-sectional analyses [21]. Although rigorous analyses were the basis for this definition, additional testing in other patient groups has not yet been performed.

Nocturia index

The nocturia index (applied in three studies) represents the nocturnal urine volume divided by the maximum voided volume. If the nocturnal volume exceeds the maximum voided volume (or functional bladder capacity), nocturia will occur. In the FVC study in asymptomatic volunteers, the nocturia index was the best predictor of nocturia [16]. However, in our opinion, this cannot be used for NP because this definition is more a measure of the association between bladder capacity and nocturnal urine volume as a possible explanation for nocturia.

Other definitions for nocturnal polyuria

The Nocturnal Bladder Capacity index (NBCi) was used in two studies. The NBCi is calculated by subtracting the predicted number of nocturnal voids from the actual number of nocturnal voids (nocturia index-1) [22]. In this definition, the problem of the first morning void (included in volume assessment but not in frequency counting) is fixed. The NBCi reflects the essence of the association between NP and nocturia. Although, strictly speaking, the NBCi is not a definition for NP it has been used as such [4]. We argue that the NBCi cannot be used as an explanatory variable for nocturnal voiding frequencies, because the formula for the NBCi incorporates the actual nocturnal voiding frequencies. However, the NBCi may well be valuable for other comparisons, such as sleep quality or quality of life.

Many of the studies included in this review only contained data on patients with nocturia. A distinction must be made between data derived from clinical samples consisting of patients suffering from bothersome symptoms of nocturia, and data from individuals showing signs without necessarily reporting them symptomatically, the latter usually originating from study populations taken from the general public. Important to notice is that in many clinical studies included in this review, it is unclear whether patients were included with bothersome symptoms of nocturia, or based on nocturnal voiding frequency without bothersome signs/symptoms. We reiterate that the definitions of illnesses or diseases should be applicable to all patients included.

Conspicuously, the ICS definitions of nocturia and NP were all based on small clinical samples. From these samples it appeared that NP (ICS definition) was the cause of nocturia in the greater majority of patients with nocturia. When applying these definitions to an unselected population it appeared that not only people with nocturia (as a symptom, not particularly bothersome), but also a majority of those without nocturia were classified as NP based on the ICS definition. Therefore, this latter casts doubt on the validity of this definition. On the other hand, other definitions have been suggested in general population based studies [21]. However, these definitions lack any validation in clinical samples. As a consequence, to date no conclusive and valid definition on NP is available

which can be recommended.

We believe that a validation procedure for the definition of NP is needed. This should include the assessment of both its discriminative value, as well as its prognostic value. Re-analyses of available databases, derived from population based samples, clinical samples, and randomised controlled trials may be suitable for this. The previously suggested definitions (other than the ICS definition) could be applied to these databases, to test their validity. This procedure should include participants with or without nocturnal voidings (as a symptom), as well as patients with or without bothersome syptoms of nocturia. Data derived from frequency-volume charts are vital for such analyses, and prospective cohort studies are the preferred study design.

Conclusions

The ICS-2002 report on the standardisation of terminology in nocturia appears to have had a beneficial impact on the reporting of definitions of nocturia and NP in relevant publications, enabling a better interpretation of results and comparisons between studies. However, all used definitions of NP lack validation procedures. The discriminative value of the ICS definition, yielding a difference of 0.6 nocturnal voidings between individuals with and without NP seems limited [9] and needs to be established in future studies using outcomes relevant to the quality of sleep and daytime performance. Refinement of current definitions based on robust research remains desirable. Based on pathophysiological reasons we argue that it may be more appropriate to define NP based on nocturnal urine production or nocturnal voided volumes rather than on a diurnal urine production pattern.

								Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
Randomised clinical trials														
XIII	1998	UK	men with nocturia	SC	Age ≥ 50, LUTS, NP	serum creatinine >150micromol/L, previous LUT surgery, symptomatic heart failure, taking medication active on the LUT including those taking any diuretic, concomitant neurological disease with could potentially affect LUT function, clinical evidence of prostate cancer, DM	49/...?	?	FVC	FVC	7	Fixed (8 PM- 8 AM)	not defined	NPi 0.33
XII	1999	UK	men with nocturia	?	Age ≥ 50, NP confirmed after 48 h of inpatient monitoring or 1 week FVC.	nocturnal enuresis or UI, significant cardiovascular, renal or hepatic disease, diabetes, UTI or concomitant medication active on the LUT	20 / ?	?	FVC	FVC	7	actual	not defined	NPi 0.33
XIV	1998 1999 2002	Sweden	men/women with nocturia	CB	people living in Stromsund and Hammerdal, Jamtland, Sweden, aged 60-74 years, healthy and free from medication with possible influence on the diuresis or voiding pattern, increased nocturnal frequency, NUP >0.9mL/min, completed and responded to initial dose titration study	receiving desmopressin treatment in 14 days before the beginning of the study, signs/symptoms/previous treatment for heart disease, hypertension, liver disease, Crohn's disease, renal or neurological problems, primary polidipsia, diabetes insipidus, UTI, medication with known interaction with desmopressin, hypersensitivity to desmopressin or AVP, current use of medication with possible effect on electrolyte metabolism, taking hypnotics or tranquillisers, drugs or alcohol abuse, smoking	23/64 (36%)	?	?	?	question-naire and 24-hr urine sample	actual	2 or more voids	NUV > 0.9 ml/ min during sleeping hours
XI	2002	?	men with nocturia	?	Age >18, nocturia, Nocturia Index scores of >1	nocturia arising from other well-defined causes of increased urinary frequency, e.g. diagnosed or suspected diabetes insipidus, primary polydipsia (40 mL/kg/24 h) or multiple sclerosis, UUI or recently commenced medical or surgical treatment for BPH; conditions characterised by fluid and/or electrolyte imbalance where anti-diuresis was inappropriate (e.g. cardiac failure, use of diuretics); serum sodium levels below the normal range, and uncontrolled hypertension. no response during dose titration and failure to return to 78% of baseline nocturnal diuresis after 1-week washout period	341 / ?	?	FVC	FVC	?	not defined	2 or more voids	NUP > max FBC

									Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
X	2003	Netherlands, Sweden, UK, USA, Denmark	women with nocturia	?	Age ≥ 18, complaining of nocturia	abnormal fluid intake, shift work, pregnancy or planned pregnancy, signs or symptoms of vaginitis or urethritis, clinically significant abnormal urine or blood values, serum sodium levels below normal range, and certain preexisting conditions (e.g. patients with diabetes insipidus, multiple sclerosis, or polydipsia [40 mL/kg per 24 h]). Overt lower urinary tract dysfunctions (eg, low bladder capacity, consistent residual volume, urge incontinence), patients receiving diuretics, tricyclic antidepressants, indomethacin, carbamazepine, or chlorpromamide. Insufficient response during dose-titration period (ie, < 20% reduction in nocturnal diuresis) or failure to return to 78% or greater of baseline nocturnal diuresis values after the 1-week washout period.	224 / ??	June 1999 - April 2000	FVC	?	?	not defined	2 or more voids	Ni > 1
IX	2004	UK	men with nocturia	?	self-reported nocturia	evidence of alternative lower urinary tract pathology (e.g. urinary tract infection, abnormal urinary cytology, suspicion or evidence of prostate cancer, chronic retention of urine, bladder stone), renal or hepatic impairment, history of surgical treatment for bladder outflow obstruction and use within the preceding month of diuretics, alpha-adrenergic antagonists, 5-alpha-reductase inhibitors, anti-depressants or sedatives.	20/...? (?%)	?	both FVC and IPSS	FVC	7	actual	3 or more voids	NPi 0.33
VIII	2006	UK	men/women with nocturia	SC	nocturia, NP, N/D Diuresis ratio 1.1 or more, Nocturia index >1	NSAID allergy or acid peptic disease, cardiac, hepatic or renal failure, Active UTI or Incontinence, Polydipsia, Urine output >3 lt/24 h, cognitive impairment, already on evening dose of NSAIDs, recent surgery <3 months	26/70 = 37%	?	FVC	FVC	7	actual	2 or more voids	NPi 0.33
VI	2007	USA, Chile	men/women with nocturia	SC/ ?	OAB (≥8 voids in 24h and UUI), nocturia who completed a RCT of tolterodine ER in the USA and Chile	polyuria (≥3,000 ml per 24 h), SUI, PVR ≥200 ml	845/850 = 99%	?	FVC	FVC	7	actual	1 or more voids	NPi 0.35
VII	**2007**	**USA**	**men/women** **with nocturia**	**?**	**Age ≥ 18, mean ≥8 voids/24h, ≥1 urgency episodes/24h**	**not defined**	**2534/ 3032 (83.%)**	**?**	**FVC**	**FVC**	**3**	**actual**	**1 or more voids**	**NUV> (no.hours of sleep/24 h)*24h**

								Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
III	2011	Japan	men/women with nocturia	?	Age ≥20, ≥6 months OAB symptoms, mean of ≥8 voids/24h, ≥3 urgency episodes, ≥3 urgency incontinence episodes in 3 day FVC	significant BOO, PVR ≥100 mL, presence of BOO symptoms, urinary retention, demonstrable SUI, bladder stones, UTI, interstitial cystitis, previous or current malignant disease of the pelvic organs, previous pelvic radiation, taking concomitant anticholinergic medications, known or suspected hypersensitivity to anticholinergic medications or lactose.	962/1191 (81%)	?	FVC	FVC	3	actual	1 or more voids	NPi without cut-off
IV	2011	China, USA	men/women with nocturia	?	Age ≥60, nocturia	nocturia due to diabetes insipidus, primary polydipsia, multiple sclerosis, UUI, consistent PVR, or evidence of urethritis, serum sodium levels below the normal range, moderate to severe renal insufficiency (creatinine clearance below 50 ml/min), syndrome of inappropriate antidiuretic hormone secretion, cardiac insufficiency, or hypersensitivity to desmopressin or furosemide	82/204 (40%)	?	FVC	FVC	7	not defined	2 or more voids	NPi 0.33
V	2011	Taiwan	men with nocturia	?	Age ≥65, BPH, nocturia, NP, IPSS ≥14	UUI, another voiding dysfunction or UTI, received treatment with drugs known or suspected to interact with desmopressin (eg diuretics, tricyclic antidepressants, indomethacin, carbamazepine or chlorpropamide), had uncontrolled hypertension and DM, or had evidence of clinically relevant cardiac failure	115/136 = 84%	October 2007 - December 2009	?	FVC	?	actual	2 or more voids	NPi 0.30
I	2012	Japan	men/women with nocturia	SC	Age ≥50, nocturia, NP	obvious neuropathic lower urinary tract dysfunction, <100 mL maximum bladder capacity, PVR >100 mL, use of furosemide, Gosha-jinki-gan, anticholinergic agents, alpha-adrenergic receptor blockers	36/...?	?	FVC	FVC	3	not defined	2 or more voids	modified NPI >33%, based on 8-h sleep period
II	2012	USA, Canada	men/women with nocturia	?	Age ≥18, nocturia, serum sodium >135 mmol/L, serum creatinine within normal limits, eGFR >60 ml/min	urinary retention and/or PVR >150 ml, or history of urologic malignancies, neurogenic detrusor activity or current genitourinary tract pathology that could interfere with voiding. Males with BOO and/or Qmax <5 ml/sec, or if surgery for BOO/BPH had been performed within 6 months. Females with potential for pregnancy, use of a pessary for pelvic prolapse, or the presence of unexplained pelvic mass	799/1412 = 57%	July 2007 - February 2008	FVC	FVC	3	actual	2 or more voids	NPi 0.33

									Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
XVI	2012	Japan	men/women with nocturia	?	Age 55-75, nocturia	bladder obstruction, Qmax <5 mL/s, surgical treatment of BOO or BPH ≤ 6 months before the study, showing symptoms of BPH, AOB or interstitial cystitis, nocturnal frequency >4 in a consecutive 3-day period during the screening, or hyponatraemia (serum sodium <135 mEq/L) after desmopressin administration.	177	July 2010 - April 2011	FVC	FVC	3	not defined	2 or more voids	NPi 0.33
XV	2013	?	men with nocturia	?	Age ≥ 45, nocturia	PVR> 250 ml, 24h urine output > 3000 ml, abnormal urinary findings suggestive of UTI, significant haematuria or glucosuria requiring further evaluation, surgical treatment for BOO/BPH < 6 mths, history of urological malignancy (e.g. bladder or prostate cancer), history or active conditions, incl known neurological diseases (e.g. cancer, renal failure, cirrhosis, chronic liver disease, pancreatic diseases, recent (< 6 mths) myocardial infarction or unstable coronary artery disease, use of medications affecting urination [e.g. loop diuretics (furosemide), antimuscarinic agents, finasteride or dutasteride], natural products used for BPH, such as saw palmetto (Sabal serrulata or Serenoa repens), known allergy or use of SagaPro or other products containing A. archangelica in 2 mths prior to randomization, patients who received investigational product within 30 days before enrolment or expected receipt during this study, interference of work or lifestyle with regular night-time sleep, e.g. shift workers.	66/?	?	FVC	FVC	3	actual	2 or more voids	NPi 0.35
Non-randomised studies														
XXXII	1998 1999	USA	men/women with/without nocturia	?	neurologically normal men with LUTS having undergone video-urodynamic studies (VUDS)	lack of voiding diaries	87/100 and 194/200	?	FVC	FVC	1	not defined	mild: 2 or less, severe 3 or more.	various definitions, including NPi 0.35 & NI >1.5
XXIX	1999	?	men with nocturia	?	BPH and nocturia	previous prostate surgery, nephrolithiasis, UTI, hematuria, DM, history of myocardial infarction, congestive heart failure, angina, alpha sympathetic agonist, alpha 1 antagonist, 5 alpha reductase, TCA's, anticholinergic agents	12/,,,?	?	?	?	?	not defined	3 or more voids	not defined

									Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
XXVIIII	2002	China	men/women with nocturia	?	severe LUTS and the symptom of nocturia, treated with imipramine or oxybutynin, or a combination, without relief of symptoms	congestive heart disease, chronic renal insufficiency, liver disease, sedatives or tranquilizers for sleep disturbances, evidence of BOO, PVR >100 ml	30 / ?	?	FVC	FVC	3	actual	3 or more voids	NPi 0.35
XXVII	2005	United Arab Emirates	men with/without nocturia	?	nocturia, no symptoms of any other diseases	not defined	14 / ?	?	?	24h urine collection	1	Fixed (8 PM- 8 AM)	2 or more voids	NPi without cut-off
XXV	2006	Turkey	men with nocturia	SC	consecutive patients aged ≥ 50, LUTS suggestive of BPH	Patients with prostate cancer, abnormal prostate findings on DRE (nodularity or induration), or PSA ≥ 10 ng/mL	40/58 (69.0%)	?	FVC	FVC	7	actual	not defined	NPi 0.33
XXVI	**2006**	**Japan**	**men** **with nocturia**	**SC/ TC**	**≥ 1 urinary urgency/day, IPSS≥8, ≥3 in any of the scores for three items (frequency, nocturia, and urgency) of IPSS**	**suspicion of prostate cancer based on DRE and PSA, any complications possibly affecting voiding function, such as neurogenic bladder, urethral stricture, active UTI and cerebrovascular diseases; any history of BPH treatment and concomitant medication such as other α1-blockers and antimuscarinic agents**	**82 / ?**	**June 2000 - December 2003**	**FVC**	**FVC**	**2**	**not defined**	**1 or more voids**	**not defined**
XXX	2008	Japan	men/women with nocturia	?	LUTS and nocturia	asthma, gastrointestinal disorders, renal dysfunction or allergies to NSAIDs	56/?	January 2003 - April 2005	FVC	FVC	?	not defined	1 or more voids	not defined
XXXI	2006 2007 2009	Japan	men/women with nocturia	SC/TC	non-neurogenic bladder, nocturia, NP	diuretic therapy, concomitant diseases such as neurogenic bladder, overt congestive cardiac failure, liver or renal dysfunction (serum creatinine >1.2 mg/dL, or a 24-h creatinine clearance <70 mL/min), DM, interstitial cystitis, UTI, or urinary incontinence frequent enough to interfere with urinary output measurement. Patients with a habitual fluid intake ≥ 100 mL at night for reasons of health, shift workers, a 24-h total urine volume (TUV) ≥40 mL/kg body weight, PVR≥50 ml	50/60 (83%) and 33/65 (51%)	August 2002 - March 2007	FVC	FVC	average 1-4 / no consecutive days	actual	1 or more voids, 3 or more	NUV >10 mol/kg body weight, NPi 0.35
XXIV	2009	Korea	men with nocturia	SC	no response or a <25% reduction in subjective nocturia using the IPSS (Q7), no response or a <25% reduction in objective nocturia according to FVC, and/ or nocturia on average 2 or more per night (according to FVC) after 4 wks terazosin therapy	reported elsewhere. additional: renal dysfunction detected by routine checkup and those with a history of renal disease	72 / 72?	May 2004 - March 2007	FVC	?	3	"according to ICS standar-disation"	2 or more voids	NPi 0.33

								Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
XXXIII	2009	USA	men with nocturia	PC	Age ≥ 50, nocturia	expected survival of ≤ 6 weeks; recent (past 2 weeks) cystoscopy or prostate biopsy; recent genitourinary surgery (past 6 months); an ongoing need to catheterize, PVR≥ 300 mL, Qmax ≤ 4 mL/s [26]; active prostate or bladder cancer; a UTI (could receive treatment and re-screen); or a neurological condition, e.g. multiple sclerosis or spinal cord injury.	55/168 = 33%	2001- 2004	FVC	FVC	3	actual	2 or more voids	NPi 0.35
XXI	2010	Korea	men/women with nocturia	?	Age ≥18, mixed nocturia (≥2 voids/night, NPi >33% and NBCi >1)	nocturia due to other defined causes of increased urinary frequency, primary polydipsia (>40 mL/kg/24 h), neurogenic bladder dysfunction, UUI, continued PVR >150 mL, serum sodium levels <135 mM/L, uncontrolled hypertension, congestive heart failure, use of diuretics, and actual or planned pregnancy	94/103 (91%)	?	FVC	?	3	actual	2 or more voids	NPi 0.33
XXII	2010	Japan	men/women with nocturia	SC	nocturia	PVR > 50 ml, untreated urogenital malignancies, or renal, cardiac or hepatic failure, strongly seeking medical treatment	56/....?	2005-2009	FVC	FVC	3	actual	2 or more voids	NPi 0.33
XXIII	2010	Japan	men with nocturia	SC	LUTS/BPH, nocturia	use of a1-receptor blocker in the previous 2 weeks and those with prostate cancer, inflammation of the prostate and the bladder, and with a lower urinary tract stone, missing FVC	160/380 (42%)	May-November 2006	FVC	FVC	3	not defined	2 or more voids	not defined
XX	2011	Japan	men with nocturia	SC	LUTS suggestive of BPH: IPSS ≥8, IPSS nocturia subscore ≥3, prostate volume ≥20 ml	medications for the control of bladder symptoms, sedatives or tranquilizers for treating sleep disturbances, neurogenic bladder dysfunction, documented history or clinical symptoms of prostatitis, prostate cancer, a history of prostate surgery or radiotherapy, or acute urinary retention.	56/...?	?	IPSS	FVC	2	not defined	3 or more voids	NPi 0.33
XVII	**2012**	**Japan**	**men/women with nocturia**	**?**	**OAB, nocturia**	**urinary tract malignancy, PVR >100 ml, bladder stone, UTI, severe heart disease, liver dysfunction, renal dysfunction, dementia. Concomitant treatment with other medications that would affect LUT function, including other anticholinergic drugs, a-adrenergic antagonists, medications for Parkinson disease and depression, and antihistaminergic drugs.**	**60/...?**	**?**	**FVC**	**FVC**	**2**	**actual**	**2 or more voids**	**NPi 0.33**
XVIII	**2012**	**Japan**	**men with/without nocturia**	**TC**	**BPH, IPSS >7, Qmax <15 ml/sec, prostate volume >20 ml**	**neuropathic disorders including DM or UTI**	**82/115 (71%)**	**2002-2008**	**both FVC and IPSS**	**FVC**	**3**	**actual**	**not defined**	**NPi 0.33**

									Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
XIX	2012	Korea	men/women with nocturia	SC	Age ≥20, nocturia, NP	diabetes insipidus, neurogenic bladder, urinary incontinence, congestive heart failure, taking diuretics for the management of hypertension, indwelling catheters, sleep disturbance, UTI, and previous surgical history of prostate or urethra	82/...?	May 2009 - March 2010	FVC	FVC	2	not defined	1 or more voids	NPi 0.33
XXXIV	2013	Korea	women with nocturia	TC	not defined	neurologic diseases, previous radical pelvic surgeries, or pelvic organ prolapses	84 / ?	January 2008- December 2011	FVC	FVC	3	not defined	2 or more voids	NPi 0.33
XXXV	2013	South Korea	men with nocturia	SC	Age ≥ 50, LUTS due to BPH, Qmax ≤ 15ml/s, nocturia, total IPSS ≥ 14 (voiding subscore ≥ 8 and storage subscore ≥ 6) with persistent nocturia after treatment with an alpha-blocker for at least 4 weeks.	neurogenic bladder dysfunction, serum sodium level <135 mM/L, uncontrolled hypertension, congestive heart failure, using diuretics	216/620-35%	April 2009 - March 2011	FVC	FVC	3	not defined	2 or more voids	NPi 0.33
Descriptive studies														
LIII	1993	Japan	men/women with/without nocturia	?	frequency	organic disorders such as BPH, neurogenic bladder, cystitis, diabetes insipidus, DM, chronic renal failure	215/...?	?	FVC	FVC	?	actual	not defined	NPi 0.35
LI	**2000**	**Japan**	**men/women** **with/without nocturia**	**SC**	**All: hospitalized patients. (asymptomatic population) apparently healthy, subjectively free of LUTS, no evidence of disorders affecting LUT function. (elderly population complaining of nocturia) nocturia, apparently healthy, free of disorders affecting LUT function**	**study 1: Qmax <10 ml/sec, PVR>30 ml study 2: not defined**	**67 + 39 / ??**	**?**	**FVC**	**FVC**	**1**	**actual**	**2 or more voids**	**NUV/body weight >10 ml/kg**
LII	2000	Japan	men with/without nocturia	CB	Age ≥55, participating in mass screening program for prostatic disease	BPH, prostatic cancer diagnosed histologically, DM, renal, heart, cerebral, vascular or psychiatric diseases, usage of sleeping pills or drugs influencing voiding or diuretic conditions	320/519 (63%)	October-November 1995	FVC	FVC	3	actual	not defined	not defined

									Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
LIX	2002	USA	women with/without nocturia	CB	ambulatory non-pregnant adult women who considered themselves to have normal lower urinary tract function.	any symptoms of UI or voiding difficulty, pelvic organ prolapse or pelvic pain, current or past use of medications with primary anticholinergic effect, relevant neurologic disorder, previous surgery for UI or pelvic organ prolapse, current vaginal pessary use, or who were working primarily at night. Positive response at Incontinence Impact Questionnaire and the Urogenital Distress Inventory	300/??	?	FVC	FVC	1	actual	both 1 and 2 or more	NPi 35%, NUV>0.9mL/min, NUV>6.4mL/kg
LX	**2002 2003**	**USA**	**men/women** **with/without nocturia**	**CB**	**age ≥ 65**	**overt and symptomatic congestive heart failure, venous insufficiency with pitting edema, DM with poor control, BOO or incomplete bladder emptying (PVR > 200 ml), anemia or UI more than once daily.**	**45/190 (24%)**	**July 1997 - September 2000**	**FVC**	**FVC**	**7**	**Fixed (11 PM - 7 AM, 11 PM - 2 AM for volumes, 11 PM-7 AM for frequency)**	**2 or more voids**	**NPi 0.35**
XLVIII	**2003**	**UK**	**women** **with/without nocturia**	**PC**	**Age ≥50, previously taken part in the prevalence study of LUTS among women registered with one family doctor practice**	**not defined**	**264/ 1183 (19.5%)**	**?**	**?**	**FVC**	**7**	**actual**	**2 or more voids**	**NPi 0.33**
XLIX	**2003**	**Sweden**	**men/women** **with/without nocturia**	**CB**	**inhabitants aged ≥65 years in Tierp, a rural community in Sweden**	**not defined**	**2866/ 4264 (67%); 290/517 (56%)/ 224/517 (43%)**	**?**	**FVC**	**FVC**	**3**	**actual**	**2 or more voids**	**NPi 0.33**
L	2003	Sweden	men with/without nocturia	SC	men hospitalized for TUR-P	cardiac disease, DM, known or suspected prostatic cancer, dementia, or indwelling catheters	15/16 snorers 11/?? Non-snorers	November 2000-February 2002	FVC	FVC	2	Fixed (11 PM- 8 AM)	not defined	not defined
XLVI	2004	Korea	women with/without nocturia	?	women referred for the evaluation of LUTS, age ≥ 20, ability to communicate, understand and comply with the study requirements.	confused state or depression, UTI, medication known to affect voiding, neurogenic bladder dysfunction, pregnancy, restricted mobility and those who were working primarily at night. Patients with an incomplete workup due to charts with missing dates, non-consecutive days or only 2 days of data	106/123 (86%)	?	IPSS	FVC	3	actual	2 or more voids	NPi 0.35

								Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
XLVII	**2004**	**Korea**	**men/women with/without nocturia**	**?**	**consecutive patients with LUTS, age ≥50, could communicate, understand and comply with the study requirements**	**confused state or depressed, used medications to control bladder symptoms, pregnancy, UTI (bacteriuria of ≥ 104 bacteria/mL of voided urine), working primarily at night, incomplete evaluation because the charts had missing dates, not consecutive days or only 2 days of data**	**104/....? (?%)**	**?**	**FVC**	**FVC**	**3**	**actual**	**1 or more, or 2 or more in 3 nights**	**NPi 0.35 & NBCi**
XLII	2005	Malaysia	men with nocturia	SC	BPH treated with a uradrenergic blocker and still having nocturia	use of diuretics, not able to understand instructions or unable to record a FVC due to social reasons	41/49= 84%	July-September 2003	FVC	FVC	3	Fixed (12 PM- 8 AM)	1 or more voids	NPi 0.33
XLIII	2005	Japan	men with/without nocturia	?	Age ≥ 50, IPSS≥ 8, QoL index ≥ 2, sleeping period between 8-9 h (noted on FVC)	neurogenic bladder disorder, prostate cancer, urethral stricture, or active UTI, as well as those who were taking medications that could influence urination or urinary output	114 / ?	April 2002-December 2003	FVC	FVC	2	actual	2 or more voids	not defined
XLIV	2005	USA	women with nocturia	TC	presenting at urogynecology clinic, nocturia and OAB symptoms such as urgency, frequency, and urge incontinence	not defined	55/60 (92%)	January 2003-November 2003	FVC	FVC	3	actual	ICS definition: once or more, for this study twice or more	modified NPi >33%, based on 8-hour sleep period
XLV	2005	Netherlands	women with/without nocturia	TC	presenting at urogynaecologic practice with complaints of urinary incontinence	not defined	111/140 (79%)	January 2002- May 2003	FVC	FVC	3	actual	2 or more voids	NPi 0.33
XL	2006	Sweden	men/women with/without nocturia	CB	members of the pensioners' association SPF in the Swedish counties of Vasterbotten and Norrbotten	not defined	6,103/ 10,216 (59,7%)	?	undefined questionnaire	?	?	not defined	not defined	"passing large amounts of urine at night"
XLI	**2006**	**Taiwan**	**men with nocturia**	**?**	**patients: nocturia. Controls: asymptomatic young men**	**history of CVA, congestive heart failure, liver disease with ascites, COPD, chronic renal insufficiency, malignancy of the genitourinary system, polydipsia, or psychogenic insomnia.**	**41 / ?**	**?**	**FVC**	**FVC**	**3**	**actual**	**2 or more voids**	**NPi 0.35**
LVI	2006	Denmark	men without nocturia	?	healthy, age 55-73	not defined	18/...?	?	FVC	FVC	7	actual	1 or more voids	not defined

									Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
XXXVII	2007	UK, Malaysia	men with nocturia	TC	Age ≥40, Asian and Caucasian ethnicity, LUTS, nocturia	Surgery for BOO, anticholinergic medication	293 / ?	July 2002-June 2005	FVC	FVC	3	actual	1 or more voids	nocturia ratio >0.2 (<60 year) or >0.3 (>60 year)
XXXVIII	2007	Korea	men/women with nocturia	?	age>20, IPSS sum>8, nocturia, able to communicate, understand, and comply with the study requirements	confused or depressed state, medications to control bladder symptoms, previous surgery for LUTS, sedatives or tranquillizers, pregnancy, UTI, urinary stones, urogenital cancer, urethral stricture, neurogenic bladder, SUI, restricted mobility, working primarily at night, and an incomplete evaluation	142/?	January-June 2005	IPSS	FVC	3	actual	1 or more voids	NPi 0.33
XXXIX	**2007**	**?**	**men** **with nocturia**	**?**	**age≥ 50, nocturia**	**past or present history of heart disease, DM with a fasting blood glucose of 200 mg/dL or more, serum Cr greater than 1.5 ng/dL, hydronephrosis, PVR≥50 ml, urinary incontinence that influenced the exact measurement of the urine volume, or UTI, habitual use of diuretics or lithium or a 24-h production ≥ 40 mL/kg body weight**	**165/ 189 = 87%**	**?**	**FVC**	**FVC**	**?**	**Fixed (10 PM – 6 AM)**	**not defined**	**NPi 0.35 and NUV > 0.9mL/ min*sleeping hours**
XXXVI	2009	Austria	men/women with nocturia	SC	nocturia	untreated UTI, PVR >200 ml, unwillingness to sign an informed consent form	324 / ?	?	?	FVC	2	not defined	2 or more voids	NPi 0.33
LV	2010	Korea	women with nocturia	TC	age>20, IPSS sum>8, nocturia (IPSS Q7)	confused or depressed mental status, medication that may alter or control bladder symptoms, symptomatic UTI, uropathologic condition (urinary stones, urogenital cancer, pelvic organ prolapsed > stage 3, neurogenic bladder, SUI stamey grade 3, restricted mobility, night working job	118/450 (26%)	January 2006-December 2008	FVC	FVC	3	actual	1 or more voids	NPi 0.35
LVII	**2009 2010**	**Japan**	**men/women** **with/without nocturia**	**CB**	**community-dwelling people who underwent mass screening program in a rural town in Hokkaido, Japan, and 75 outpatients who consulted the Dept of Urology, Meiji University of Integrative Medicine, with various complaints incl nocturia**	**24-hour polyuria (>40mL/kg), suspected of suffering from definite pathological disorders such as cancer of the bladder, bladder stone, bacterial cystitis, cancer of the prostate and prostatitis, no completed bladder diary, no consent to participate in the study**	**450/ 694**	**April 2005 - December 2006**	**FVC**	**FVC**	**3**	**actual**	**mild: 1, severe 2 or more. Ref 142: 1 or more**	**Proportion NUP rate (ml/min) / datyime UP rate > 1 , NPi 0.33**

								Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
LVIII	2007 2011	UK, USA	men/women with/without nocturia	SC	controls: not stated, patients: LUTS	LUTS and disorders, medications, and surgeries that might affect urination, (e.g. DM, heart disease, neurologic disorders), and previous incontinence surgery, non-standard sleep patterns (e.g., night shifts), if a standardized questionnaire revealed bladder symptoms, previous urological or continence surgery, medications influencing bladder habits and a night-shift sleep pattern, if diaries contained one or more incontinence episodes, recording of volumes of only 25% or less of all voids or recording of only 10% or less of all night voids.	161+92 /...?	?	FVC	FVC	3	actual	1 or more voids	NBCi, NPi without cut off
LXI	**2000 2002 2012**	**Netherlands**	**men with/without nocturia**	**CB**	**Community-dwelling men living in Krimpen aan den IJssel, the Netherlands, aged 50-75 years, filled in FVC**	**previous transurethral or open prostatectomy, prostate or bladder cancer, neurogenic bladder disease, or negative advice from their primary care physician (PCP) based on poor health (e.g., being bedridden).**	**1396/1597 = 87%, 1688/3942 (50%)**	**1995-1997**	**both FVC and IPSS**	**FVC**	**3 day FVC (1-day volume)**	**fixed for NP - actual for nocturia***	**nocturia 2 (2 or more) and nocturia 3 (3 or more)**	**various definitions (NPi 0.33, NUP>90 ml/h)**
LIV	2012	Netherlands	men/women with/without nocturia	CB	Adult volunteers without a urological complaint or a urological history, recruited from hospital staff and families, and patients' families.	25% of sleeping time exceeded between time of rising and first morning void, missing first morning void on FVC	894/1152 (78%)	?	FVC	FVC	1	actual	1, 2 or more than 2	NPi 0.53
Case control studies														
LXIV	1998	Italy	men with/without nocturia	SC	all: submitted to open or transurethral ablation of an obstructive BPH. Patients: nocturia without symptoms related to residual bladder instability. Controls: complete resolution of nocturia (or max one void/night) one year post-operatively	associated symptoms related to residual bladder instability, history of ischaemic heart disease, congestive heart failure, mild or severe hypertension, diuretic or other antihypertensive therapies.	12/27 (44%)	?	?	?	24 h urinary volume	Fixed (8 PM - 8 AM)	not defined	not defined
LXV	**1999 2003**	**Denmark**	**men with/without nocturia**	**SC/TC**	**patients: consecutively referred to department with LUTS for BPH evaluation & age-matched controls with no history of nocturia or any other urological complaints**	**All: abnormalities on physical examination, history of renal, cardiac or hepatic disease, abnormal clinical blood pressure, bacteriuria, proteinuria and glucosuria. Controls: Qmax < 14 mL/s**	**11 + 23 / ??**	**?**	**FVC**	**FVC**	**7**	**actual**	**not defined**	**NUP > 2 SD of the mean (of the controls)**

								Measurement method		FVC length	Applied definitions		
Study nr.	Year	Country	Participants	Origin	Inclusion criteria	Exclusion criteria	No. (%)	Study period	Nocturia	NP	(days)	night	Nocturia	NP
LXIII	2005	Japan	men/women with/without nocturia	SC	patients: nocturia as principal complaint at urologic consult, controls: age-gender matched volunteers without nocturia	active lower UTI, active lower urinary tract calculi, active bladder cancer, or locally advanced prostate cancer	110/117 (94%)	November 2002 - March 2004	IPSS	FVC	2	actual	mild 3 or less, severe 4 or more	NUV/ total volume > time spent in bed/24 h
LXII	2011	UK	men/women with/without nocturia	?	control: standard sleep pattern, good health patients: under investigation for sleep-disordered breathing by a standard sleep study attending the Gwent Sleep Centre	patients: not stated control: night shift workers	89+21/….?	?	FVC	FVC	1	actual	not defined	NPi without cut-off
LXVI	**2007 2012**	**Denmark**	**men/women** **with/without nocturia**	**CB**	**respondents in a population study of 4,000 men/women 60-80 years old, answering a question on nocturia**	**night shift work, severe physical disability, or mental impairment (dementia) and inability to follow instructions.**	**150 / 1111 (13,5%)**	**January 2003 - January 2005**	**FVC**	**FVC**	**3**	**actual**	**2 or more voids**	**NPi 0.33**

Table 1. Characteristics of the included studies.
Study numbers refer to Appendix A. References printed bold are included in Chapter 2 for the meta analyses [9].
All ages are in 'years'. Abbreviations: BMI: body mass index; BOO: bladder outlet obstruction; BP: blood pressure; BPH: benign prostate hyperplasia; CB: community based; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; DM: diabetes mellitus; DRE: digital rectal examination; FVC: frequency volume chart; ICS: Internal Continence Society; LUT: lower urinary tract; LUTS: lower urinary tract symptoms; NBCi: Nocturnal Bladder Capacity index; NP: nocturnal polyuria; OAB: overactive bladder; PC: primary care; PVR: post void residual volume; Qmax: maximal urinary flow rate; SC: secondary care; SUI: stress urinary incontinence; T: temperature; TC: tertiary care; UTI: urinary tract infection; UUI: urge urinary incontinence

Appendix A. Bibliographic information on the studies included in this systematic review.
Those studies that were used in the meta-analysis are bolded.

Study nr	References included and used for quality assessment and data extraction
I	Yoshimura K, Shimizu Y, Masui K, et al. Furosemide versus Gosha-Jinki-Gan, a Blended Herbal Medicine, for Nocturnal Polyuria: A Randomized Crossover Trial. *LUTS* 2012; 4 (2): 77-81.
II	Weiss JP, Zinner NR, Klein BM, Norgaard JP. Desmopressin orally disintegrating tablet effectively reduces nocturia: Results of a randomized, double-blind, placebo-controlled trial. *Neurourol Urodyn* 2012; 31 (4): 441-7.
III	Yokoyama O, Yamaguchi O, Kakizaki H, et al. Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: Impact on sleep evaluated by bladder diary. *J Urol* 2011; 186 (1): 170-4.
IV	FG, Lavery HJ, Wu DL. Reducing nocturia in the elderly: A randomized placebo-controlled trial of staggered furosemide and desmopressin. *Neurourol Urodyn* 2011; 30 (3): 312-6.
V	Wang CJ, Lin YN, Huang SW, Chang CH. Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: A double-blind, placebo controlled, randomized study. *J Urol* 2011; 185 (1): 219-23.
VI	Weiss JP, Blaivas JG, Jones M, Wang JT, Guan Z. Age Related Pathogenesis of Nocturia in Patients With Overactive Bladder. *J Urol* 2007; 178 (2): 548-51
VII	Brubaker L, FitzGerald MP. Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. *Int Urogynecol J Pel* 2007; 18 (7): 737-41.
VIII	Addla SK, Adeyoju AB, Neilson D, O'Reilly P. Diclofenac for treatment of nocturia caused by nocturnal polyuria: A prospective, randomised, double-blind, placebo-controlled crossover study. *Eur Urol* 2006; 49 (4): 720-5.
IX	Drake MJ, Mills IW, Noble JG. Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. *J Urol* 2004; 171 (3): 1199-202.
X	Lose G, Lalos O, Freeman RM, Van Kerrebroeck P. Efficacy of desmopressin (Minrin) in the treatment of nocturia: A double-blind placebo-controlled study in women. *Am J Obstet Gynecol* 2003; 189 (4): 1106-13.
XI	Mattiasson A, Abrams P, Van Kerrebroeck P, Walter S, Weiss J. Efficacy of desmopressin in the treatment of nocturia: A double-blind placebo-controlled study in men. *BJU Int* 2002; 89 (9): 855-62.
XII	Cannon A, Carter PG, McConnell AA, Abrams P. Desmopressin in the treatment of nocturnal polyuria in the male. *BJU Int* 1999; 84 (1): 20-4.
XIII	Reynard JM, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: A double-blind randomized trial of frusemide against placebo. *BJU 1998*; 81 (2): 215-8.

Study nr	References included and used for quality assessment and data extraction
XIV	Asplund R, Sundberg B, Bengtsson P. Desmopressin for the treatment of nocturnal polyuria in the elderly: A dose titration study. *Brit J Urol 1998*; 82 (5): 642-6.
	Asplund R, Sundberg B, Bengtsson P. Oral desmopressin for nocturnal polyuria in elderly subjects: A double-blind, placebo-controlled randomized exploratory study. *BJU Int* 1999; 83 (6): 591-5.
	Asplund R. Diuresis pattern, plasma vasopressin and blood pressure in healthy elderly persons with nocturia and nocturnal polyuria. *Neth J Med* 2002; 60 (7): 276-80.
XV	Sigurdsson S, Geirsson G, Gudmundsdottir H, Egilsdottir PB, Gudbjarnason S. A parallel, randomized, double-blind, placebo-controlled study to investigate the effect of SagaPro on nocturia in men. *Scand J Urol* 2013; 47 (1): 26-32.
XVI	Yamaguchi O, Nishizawa O, Juul KV, Norgaard JP. Gender difference in efficacy and dose response in Japanese patients with nocturia treated with four different doses of desmopressin orally disintegrating tablet in a randomized, placebo-controlled trial. *BJU Int* 2013; 111 (3): 474-84.
XVII	Wada N, Watanabe M, Kita M, et al. Effect of Imidafenacin on Nocturia and Sleep Disorder in Patients with Overactive Bladder. *Urol Int* 2012; 89 (2): 215-21.
XVIII	Kojima Y, Sasaki S, Imura M, Kubota Y, Hayashi Y, Kohri K. Tamsulosin reduces nighttime urine production in benign prostatic hyperplasia patients with nocturnal polyuria: A prospective open-label long-term study using frequency-volume chart. *Neurourol Urodyn* 2012; 31 (1): 80-5.
XIX	Cho SY, Lee SL, Kim IS, Koo DH, Kim HJ, Oh SJ. Short-term effects of systematized behavioral modification program for nocturia: A prospective study. *Neurourol Urodyn* 2012; 31 (1): 64-8.
XX	Yokoyama O, Aoki Y, Tsujimura A, Takao T, Namiki M, Okuyama A. (alpha)1-Adrenoceptor blocker naftopidil improves sleep disturbance with reduction in nocturnal urine volume. *World J Urol* 2011; 29 (2): 233-8.
XXI	Lee HW, Choo MS, Lee JG, et al. Desmopressin is an effective treatment for mixed nocturia with nocturnal polyuria and decreased nocturnal bladder capacity. *J Korean Med Sci* 2010; 25 (12): 1792-7.
XXII	Soda T, Masui K, Okuno H, Terai A, Ogawa O, Yoshimura K. Efficacy of nondrug lifestyle measures for the treatment of nocturia. *J Urol* 2010; 184 (3): 1000-4.
XXIII	Yoshida M, Inadome A, Masunaga K, Nagata T, Yoshiyasu T. Effectiveness of tamsulosin hydrochloride and its mechanism in improving nocturia associated with lower urinary tract symptoms/benign prostatic hyperplasia. *Neurourol Urodyn* 2010; 29 (7): 1276-81.
XXIV	Cho MC, Ku JH, Paick JS. (alpha)-Blocker Plus Diuretic Combination Therapy as Second-line Treatment for Nocturia in Men With LUTS: A Pilot Study. *Urology* 2009; 73 (3): 549-53.
XXV	Koseoglu H, Aslan G, Ozdemir I, Esen A. Nocturnal polyuria in patients with lower urinary tract symptoms and response to alpha-blocker therapy. *Urology* 2006; 67 (6): 1188-92.
XXVI	Takahashi S, Tajima A, Matsushima H, Kawamura T, Tominaga T, Kitamura T. Clinical efficacy of an (alpha)1A/D-adrenoceptor blocker (naftopidil) on overactive bladder symptoms in patients with benign prostatic hyperplasia. *Int J Urol* 2006; 13 (1): 15-20.
XXVII	Al-Waili NS, Al-Waili TN, Al-Waili AN, Saloom KY. Urinary nitrite excretion and urinary variables in patients with primary nocturnal frequency of micturition: Effects of indomethacin suppositories. *World J Urol* 2005; 23 (4): 287-94.

Study nr	References included and used for quality assessment and data extraction
XXVIII	Kuo HC. Efficacy of desmopressin in treatment of refractory nocturia in patients older than 65 years. *Urology* 2002; 59 (4): 485-9.
XXIX	Chancellor MB, Atan A, Rivas DA, Watanabe T, Tai HL, Kumon H. Beneficial effect of intranasal desmopressin for men with benign prostatic hyperplasia and nocturia: Preliminary results. *Techniques in Urology* 1999; 5 (4): 191-4.
XXX	Araki T, Yokoyama T, Araki M, Furuya S. A clinical investigation of the mechanism of loxoprofen, a non-steroidal anti-inflammatory drug, for patients with nocturia. *Acta Med Okayama* 2008; 62 (6): 373-8.
XXXI	Natsume O. A Clinical Investigation of Nocturnal Polyuria in Patients With Nocturia: A Diurnal Variation in Arginine Vasopressin Secretion and its Relevance to Mean Blood Pressure. *J Urol* 2006; 176 (2): 660-4.
	Natsume O. Diuretic pattern in adults with nocturnal polyuria: The possible contribution of blood pressure to the worsening of nocturnal polyuria. *Int J Urol* 2007; 14 (9): 822-7.
	Natsume O, Kaneko Y, Hirayama A, Fujimoto K, Hirao Y. Fluid control in elderly patients with nocturia. *Int J Urol* 2009; 16 (3): 307-13.
XXXII	Weiss JP, Blaivas JG, Stember DS, Brooks MM. Nocturia in adults: Etiology and classification. *Neurourol Urodynam* 1998; 17 (5): 467-72.
	Weiss JP, Blaivas JG, Stember DS, Chaikin DC. Evaluation of the etiology of nocturia in men: The nocturia and nocturnal bladder capacity indices. *Neurourol Urodyn* 1999; 18 (6): 559-65.
XXXIII	Vaughan CP, Endeshaw Y, Nagamia Z, Ouslander JG, Johnson TM. A multicomponent behavioural and drug intervention for nocturia in elderly men: Rationale and pilot results. *BJU Int* 2009; 104 (1): 69-74.
XXXIV	Jeong JY, Kim SJ, Cho HJ, et al. Influence of type of nocturia and lower urinary tract symptoms on therapeutic outcome in women treated with desmopressin. *Korean J Urol* 2013; 54 (2): 95-9.
XXXV	Bae WJ, Bae JH, Kims SW, et al. Desmopressin add-on therapy for refractory nocturia in men receiving alpha-blockers for lower urinary tract symptoms. *J Urol* 2013; 190 (1): 180-6.
XXXVI	Klingler HC, Heidler H, Madersbacher H, Primus G. Nocturia: An Austrian study on the multifactorial etiology of this symptom. *Neurourol Urodyn* 2009; 28 (5): 427-31.
XXXVII	Mariappan P, Turner KJ, Sothilingam S, Rajan P, Sundram M, Stewart LH. Nocturia, nocturia indices and variables from frequency-volume charts are significantly different in Asian and Caucasian men with lower urinary tract symptoms: A prospective comparison study. *BJU Int* 2007; 100 (2): 332-6.
XXXVIII	Paick JS, Kim SW, Oh SJ, Ku JH. Voiding patterns in men and women with lower urinary tract symptoms combined with nocturia. *Int J Urol* 2007; 14 (8): 699-703.
XXXIX	Akiyama T, Hirayama A, Fujimoto K, Torimoto K, Yoshida K, Hirao Y. Cutoff Value of Urinary Arginine Vasopressin for Nocturnal Polyuria in Elderly Men. *Urology* 2007; 69 (1): 98-102.
XL	Asplund R. Hip fractures, nocturia, and nocturnal polyuria in the elderly. *Arch Gerontol Geriat* 2006; 43 (3): 319-26.
XLI	Chang SC, Lin ATL, Chen KK, Chang LS. Multifactorial nature of male nocturia. *Urology* 2006; 67 (3): 541-4.

Study nr	References included and used for quality assessment and data extraction
XLII	Yoong HF, Sundaram MB, Aida Z. Prevalence of nocturnal polyuria in patients with benign prostatic hyperplasia. *Med J Malaysia* 2005; 60 (3): 294-6.
XLIII	Hirayama A, Fujimoto K, Matsumoto Y, Hirao Y. Nocturia in men with lower urinary tract symptoms is associated with both nocturnal polyuria and detrusor overactivity with positive response to ice water test. *Urology* 2005; 65 (6): 1064-9.
XLIV	Drake NL, Flynn MK, Romero AA, Weidner AC, Amundsen CL. Nocturnal polyuria in women with overactive bladder symptoms and nocturia. *Am J Obstet Gynecol* 2005; 192 (5): 1682-6.
XLV	Massolt ET, Wooning MM, Stijnen T, Vierhout ME. Prevalence, impact on the quality of life and pathophysiological determinants of nocturia in urinary incontinent women. *Int Urogynecol J Pel* 2005; 16 (2): 132-7.
XLVI	Ku JH, Lim DJ, Byun SS, Paick JS, Oh SJ. Nocturia and complementary indices: Determination and quantification of the cause of nocturia by frequency-volume charts in women with lower urinary tract symptoms. *Urol Res* 2004; 32 (3): 181-4.
XLVII	Ku JH, Lim DJ, Byun SS, Paick JS, Oh SJ. Nocturia in patients with lower urinary tract symptoms: Association with diurnal voiding patterns. *BJU Int* 2004; 93 (7): 1005-8.
XLVIII	Swithinbank LV, Vestey S, Abrams P. Nocturnal polyuria in community-dwelling women. *BJU Int* 2003; 93 (4): 523-7.
XLIX	Rembratt A, Norgaard JP, Andersson KE. Differences between nocturics and non-nocturics in voiding patterns: An analysis of frequency-volume charts from community-dwelling elderly. *BJU Int*, Suppl 2003; 91 (1): 45-50.
L	Kinn AC, Harlid R. Snoring as a cause of nocturia in men with lower urinary tract symptoms. *Eur Urol* 2003; 43 (6): 696-701.
LI	Homma Y, Yamaguchi O, Kageyama S, Nishizawa O, Yoshida M, Kawabe K. Nocturia in the adult: Classification on the basis of largest voided volume and nocturnal urine production. *J Urol* 2000; 163 (3): 777-81.
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PART II

Enuresis, nocturnal polyuria and functional bladder capacity: focus on definitions

CHAPTER 4

Reference values for frequency volume chart and uroflowmetry parameters in adolescent and adult enuresis patients

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Abstract

Introduction

Reference values of Frequency Volume Chart (FVC) and uroflowmetry parameters for adolescent and adult enuresis patients are lacking. In this study, we aim to describe those parameters, in order to interpret findings from FVCs and uroflowmetries in those patients.

Methods

Retrospective, descriptive cohort study, concerning 907 patients aged 11 years and older, suffering from enuresis of at least one wet night per fortnight, treated in a secondary/tertiary centre, between 2003 and 2013. The main FVC parameters of interest were: maximum voided volume (MVV), 24h urine production and nocturnal urine volume (NUV) including first morning void (FMV). Nocturnal polyuria (NP) was defined based on both International Children's Continence Society (ICCS, 2014) and International Continence Society (ICS, 2002) definitions. Data of all patients were collected from the medical files.

Results

Age had an impact on diurnal and nocturnal FVC parameters. Median MVV excluding FMV was 250 ml in the youngest, 11-yr-old males and 363 ml in the eldest, ≥18-yr-old males. For females, these values were 230 ml and 310 ml. Median 24h urine production increased from 1,025 ml to 1,502 ml (males) and from 1,007 ml to 1,557 ml (females). Median NUV showed an increase from 387 ml to 519 ml (males) and from 393 ml to 525 (females). Forty-two percent of men and 30% of women had a small MVV (for age). Prevalence of NP differed when assessed by the ICS or the ICCS definition: following ICS guidelines, NP was present in 96% of our male and 93% of our female population, compared to 27% and 41%, respectively, following ICCS guidelines.

Conclusions

Both small MVV and NP were found frequently in our adolescent and adult enuresis patients, which is in line with the current thoughts on causal factors. NP prevalence is quite different when using ICS or ICCS definitions, respectively. We would like to encourage the development of an unambiguous definition of NP to use both in paediatric and adult urology.

Introduction

Enuresis has three main causal factors: nocturnal polyuria (NP), small bladder capacity (small maximum voided volume, MVV), and arousal problems [1]. Frequency Volume Charts (FVCs) are recommended as an important diagnostic tool in patients with enuresis, providing information on NP and bladder capacity. Findings on FVCs should be compared to reference values, which are available for children 6 – 11 years of age [2], but appear to be lacking for adolescents and adults. Reference values for uroflowmetry are available for the normal population [3], and have been described for children aged 6 – 15 years with daytime and night-time wetting [4], but appear to be lacking for older adolescents as well.

NP is generally defined as a nocturnal overproduction of urine. The actual definitions, as currently stated by the International Children's Continence Society (ICCS, 2014) and the International Continence Society (ICS, 2002), differ for children and adults. For adults, the ICS defined NP as a nocturnal urine production exceeding 20-33% (age-dependent) of the 24-hour voided volume [5]. For children, the ICCS applies a different definition, in which both nocturnal urine production and bladder capacity are used [6]. This is comparable to the nocturnal bladder capacity index, as introduced by Weiss et al. [7]. The ICCS defines NP to be present when the nocturnal urine volume exceeds 130% of the expected bladder capacity (EBC) for age. EBC is defined for children aged 4-12 years as (age in years +1)*30 and is expressed in millilitres [8]. Recently, the validity of this NP formula was questioned and a new formula was proposed, representing the 97.5 percentile in a normal paediatric population: nocturnal urine volume greater than 20 x (age + 9) ml [9]. The adolescent age group is not captured in either definition.

Reference values for nocturnal urine volumes, bladder capacity and uroflowmetry are lacking for adolescents and young adults with enuresis. In order to interpret findings from FVCs and uroflowmetry in adolescents and adults with enuresis, we aimed to describe reference values, based on current ICS and ICCS definitions, in adolescents and adults with enuresis treated in a secondary care center.

Methods

Patient selection

A retrospective, descriptive cohort study was performed in 907 adolescent and adult patients with enuresis of at least one wet night per fortnight, aged 11-42 years at initial visit to the outpatient department, of which 81% had non-monosymptomatic enuresis (NMNE), treated with Adapted Dry Bed Training (Adapted DBT) in the Dry Bed Centre, a specialised enuresis centre, from 2003-2013.

Treatment

Patient descriptives, content of Adapted DBT and its treatment results are described elsewhere [10]. In brief, Adapted DBT is a 5-days/4-nights in-hospital group-training consisting of a patient history on enuresis, explanation, alarm treatment, day-time activities with the purpose of increasing self-esteem

and group contact. Follow-up was performed by telephone until six months after the initial training. Before Adapted DBT was initiated, all patients filled in a 3-day FVC, and underwent uroflowmetry, followed by post voiding residual (PVR) volume measurement by abdominal ultrasonography.

Data collection

Data collection is described elsewhere [10]. In brief, data were derived from written medical charts and manually entered in a database (Research Manager®). Duplicate subtraction was performed for 10% of all files, in order to prevent errors. When uroflowmetry was performed more than once at the initial visit to the outpatient clinic, the uroflowmetry with the largest volume was used in the analysis.

Outcome parameters

The main parameters of interest were as follows: maximum voided volume (MVV), average voided volume (AVV), voiding frequency, 24h urine production and nocturnal urine volume including first morning void (FMV) (as described by patients themselves, as no time of rise and going to bed were registered). Small bladder capacity (small MVV) was defined according to the ICCS definition of MVV <65% of EBC. For all study participants aged ≥ 12 years, EBC was defined as 390 ml [6]. The nocturnal polyuria index (NPi) was calculated by dividing nocturnal urine production by 24h urine production. Presence of nocturnal polyuria was defined in two different ways:
1. ICS definition: NPi > 0.20, as only young patients are included in our study [5];
2. ICCS definition: NUP > 130% of the EBC [6].

We calculated the MVV during the day in two ways: including the FMV and excluding the FMV. The latter is in line with former research. In a study of 148 children without enuresis, aged 3-15 years, using 4-day FVCs, the MVV with the FMV was significantly higher than without the FMV [9]. The 50th percentile without the FMV gave values identical to Koff's formula of (age in years +1)*30 [9].

Statistical analysis

Descriptive univariate analyses of FVC parameters using available case analyses were conducted, by using pairwise deletion of those cases that have missing values of the variables of interest for that particular analysis. This resulted in three different subset-analyses with, consequently, a different number of patients due to missing values: (1) analyses of diurnal FVC parameters, including all patients with three FVC's, two or more outputs and no missing voiding times. (2) analyses of nocturnal FVC parameters, including all aforementioned patients who also had three filled in nocturnal urinary volumes in the FVC. (3) analyses of uroflowmetry parameters, including all patients with available voided volume and post voiding residual volume (PVR) measurement. For each subset-analysis, the age and gender-distribution were assessed, comparing the included group to the excluded group, by Mann Whitney U and Chi-square testing, to assess whether any selection bias was present.

Results are expressed in median and interquartile ranges (IQR), as we want to show the proportional distribution of the different values in our population. Results are presented in different age groups: 11 years, 12-14, 15-17 and >18 years. Our rationale here is that Koff's formula for EBC is applicable until 11 years of age, and we wanted to separate the adult from the adolescent group as well.

We decided to present reference values, as found in this population, without statistical testing of possible differences according to age or gender. As we faced missing values, we did however test possible differences between in- and excluded groups, to see if data were missing at random or not.

The ICCS and ICS nocturnal polyuria measures – percentage of EBC and the NPi– are additionally analyzed for enuresis severity, over the different age groups. Enuresis severity was categorized after ICCS definitions, as frequent (≥ 4 days/week) or infrequent (<4 days/week) [6]. The reported p-values are two-sided and a p-value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 22.

		11 years	12-14 years	15-17 years	≥ 18 years	All
Diurnal FVC parameters (N=581)		*N=92*	*N=261*	*N=129*	*N=99*	
MVV incl FMV	M	250 [200-300]	300 [250-380]	375 [300-500]	425 [300-555]	
(mL) (med, IQR]	F	275 [200-350]	300 [240-400]	400 [300-470]	375 [300-430]	
Small MVV, incl	M	38	32	17	19	29
FMV (%)	F	39	32	14	16	23
MVV excl FMV	M	250 [200-300]	275 [220-315]	350 [250-400]	363 [250-500]	
(mL) (med, IQR]	F	230 [200-300]	300 [200-350]	378 [300-450]	310 [280-400]	
Small MVV, excl	M	49	47	27	27	42
FMV (%)	F	52	40	16	23	30
AVV	M	140 [109-162]	169 [133-203]	213 [179-253]	235 [185-270]	
(mL) [med, IQR]	F	148 [124-196]	173 [139-214]	218 [170-260]	202 [154-230]	
FMV	M	157 [125-197]	190 [147-250]	267 [197-317]	273 [197-400]	
(mL) [med, IQR]	F	167 [140-200]	192 [150-269]	233 [190-283]	233 [187-297]	
Voiding frequency	M	6 [5-7]	5.3 [4.3-6.3]	5.3 [4.7-6]	5.7 [5-7.3]	
(nr) [med, IQR]	F	6 [4.7-6.3]	5.5 [4.3-6.3]	5 [4.2-6.7]	6.3 [5-8]	
Nocturnal FVC parameters (N=390)		*N=75*	*N=179*	*N=72*	*N=64*	
24hr volume	M	1025 [865-1253]	1113 [903-1350]	1334 [1128-1591]	1502 [1042-2260]	
(mL) [med, IQR]	F	1007 [916-1252]	1117 [933-1282]	1265 [973-1517]	1557 [1243-1934]	
Nocturnal volume	M	387 [287-470]	400 [283-488]	450 [367-567]	519 [267-630]	
(mL) [med, IQR]	F	392 [357-500]	428 [318-555]	410 [252-520]	525 [362-683]	
NPi	M	.37 [.31-.42]	.35 [.28-.43]	.33 [.30-.39]	.30 [.26-.35]	
(mL) [med, IQR]	F	.40 [.37-.47]	.37 [.30-.43]	.32 [.23-.38]	.33 [.26-.41]	
NP –	M	26	22	36	53	27
ICCS definition (%)	F	35	31	32	55	41
NP –	M	93	96	100	93	96
ICS definition [%)	F	88	100	88	92	93
Uroflowmetry (N=589)		*N=88*	*N=275*	*N=135*	*N=91*	
Voided volume	M	221 [155-284]	263 [184-338]	330 [246-442]	283 [157-400]	
(mL) [med, IQR]	F	269 [205-323]	313 [179-402]	276 [220-459]	283 [193-395]	
PVR	M	0 [0-10]	0 [0-15]	0 [0-10]	0 [0-0]	
(mL) [med, IQR]	F	0 [0-5]	0 [0-13]	10 [0-30]	0 [0-10]	
Bladder capacity	M	231 [160-290]	273 [190-350]	347 [246-442]	283 [157-412]	
(mL) [med, IQR]	F	270 [204-328]	319 [189-414]	287 [220-466]	285 [204-403]	
Qmax	M	24 [18-28]	28 [22-35]	33 [27-41]	28 [21-32]	
(mL/s) [med, IQR]	F	34 [26-42]	36 [29-48]	38 [29-47]	38 [24-47]	

Table 1. Frequency volume chart and uroflowmetry parameters for age-groups and gender.
Abbreviations: AVV: Average Voided Volume, FMV: First Morning Void, FVC: Frequency Volume Chart, ICCS: International Children's Continence Society, ICS: International Continence Society, IQR: Interquartile Range, MVV: Maximum Voided Volume, NP: Nocturnal Polyuria, NPi: Nocturnal Polyuria index, PVR: post voiding residue, Qmax: maximum urinary flow rate in ml/sec

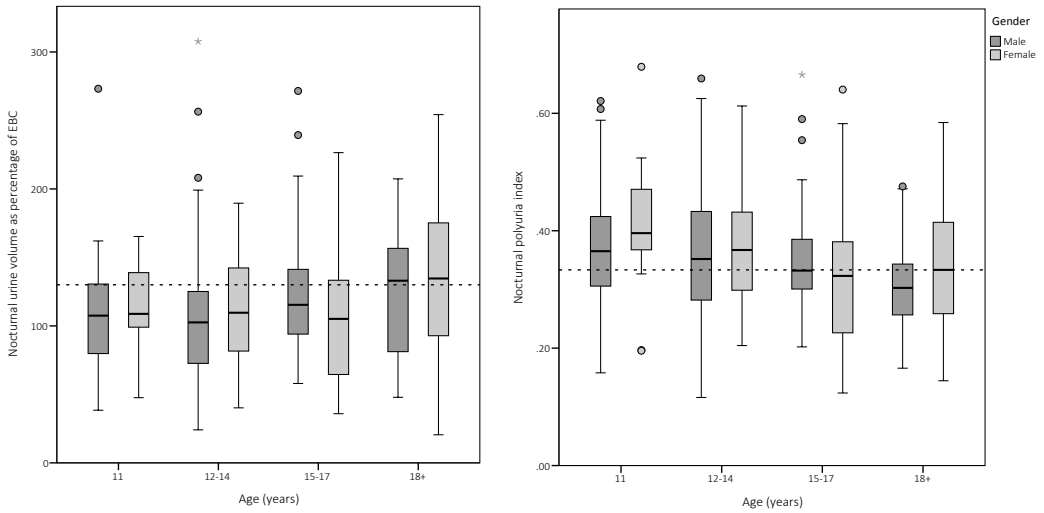

Figure 1. Nocturnal polyuria according to ICCS and ICS definitions.
Nocturnal urine volume for the different age groups, as measured by frequency volume chart, in Box-Whisker plots (median and interquartile ranges).
Left: expressed as a percentage of the Expected Bladder Capacity (EBC). Right: expressed as the Nocturnal Polyuria index (right).
The dashed lines indicate the cut-off points for the definition of nocturnal polyuria, according to ICCS (middle) and ICS (right) definitions. The circles above and below the box whisker plots represent outliers.

Results

Diurnal FVC parameters

For the analysis of the diurnal FVC parameters, 581 patients were available. Median age was 14 years [IQR 12-16], 66% males. The excluded patients had a significant lower median age (13 years [IQR 11-15], p<0.001), the gender distribution was not significantly different (70% males). All daytime parameters for the different age groups are expressed in Table 1: MVV, AVV, FMV and voiding frequency. Both MVV, AVV and FMV increased over the age groups. Small MVV (excluding FMV) for age was present in 42% of men and 30% of women, a gender difference of this magnitude is mainly present in the age groups between 12 and 14 and between 15 and 17 years (47 vs 40 and 27 vs 16, respectively). When including the FMV, small MVV for age was present in 29% of males and 23% of females when considering the whole population.

Nocturnal FVC parameters

For the analysis of the nocturnal FVC parameters, 390 patients were available. Median age was 13 years [IQR 12-16], 66% males. The excluded patients had a significant lower median age of 13 [IQR 11-15] years, p=0.014. Table 1 shows an increase of 24hour voided volume, nocturnal urinary volume and NPi over the age groups for both genders. Table 2 shows the nocturnal polyuria measures for the different age groups categorized by enuresis severity (infrequent versus frequent enuresis).
Following ICS guidelines, NP was present in 96% of our male and 93% of our female population. Following ICCS guidelines, NP was present in 27% of males and 41% of females, differing slightly between gender and the different age groups (Table 1, Figure 1).

Nocturnal polyuria		11 years *N=71*	12-14 years *N=164*	15-17 years *N=64*	≥ 18 years *N=57*	Total *N=356*
Percentage of EBC (ICCS) (med, IQR]	*Infrequent enuresis*	109.2 [97.5-133.2]	90.0 [70.1-120.3]	105.6 [84.2-145.3]	107.5 [72.7-175.2]	105.1 [78.7-142.4]
	Frequent enuresis	107.6 [80.6-134.3]	108.3 [79.2-131.0]	109.8 [82.5-136.8]	147.3 [94.0-177.4]	109.7 [81.8-141.0]
Nocturnal polyuria index (ICS) (med, IQR]	*Infrequent enuresis*	.45 [.36-.51]	.33 [.28-.39]	.33 [.30-.39]	.30 [.24-.35]	.33 [.28-.40]
	Frequent enuresis	.37 [.32-.42]	.37 [.29-.45]	.33 [.25-.36]	.34 [.28-.46]	.35 [.29-.43]

Table 2. Nocturnal polyuria measures for age-groups and degree of enuresis.
Abbreviations: EBC: Expected Bladder Capacity, ICCS: International Children's Continence Society, ICS: International Continence Society, IQR: Interquartile Range

Uroflowmetry parameters

For the analysis of the uroflowmetry parameters, 589 patients were available. Median age was 14 years [IQR 12-16], 65% males. Age nor gender distribution were significantly different between included and excluded patients. Uroflowmetry parameters, being voided volume, PVR, bladder capacity (PVR added to voided volume) and maximum urinary flow rate (Qmax) are expressed in Table 1, showing that PVR most often was zero milliliters.

Discussion

In this article, we attempt to provide reference values for this specific population of adolescents and adults with enuresis. MVV and 24h voided volumes showed a clear increase with advancing age, which is comparable to the normal population. The most important finding, in our opinion, is the large disagreement found between NP-prevalences, as defined by the ICS or the ICCS.

Nocturnal polyuria

The ICCS has defined NP as a nocturnal urine output exceeding 130% of the EBC for a specific age [6], and recommended reporting of actual nocturnal urine output and EBC's as well. In comparison, the ICS has defined NP as age-dependent in a categorical way: a nocturnal urine volume of more than 20-30% of total 24 hour urine volume [5]. In our male population, 27% or 96% of patients have NP, according to ICCS or ICS criteria, respectively. In women, this accounted for 41 and 93%. This large difference is noteworthy. The accuracy of the NP definition in adults has been questioned before [11]. The NPi is known to be affected by age [5]. Although the absolute increment is small in our population, when considering age differences, the increase is still considerable.

Both the percentage of EBC and the NPi differ for infrequent and frequent enuresis among most age groups. However, all IQRs show substantial overlap. Therefore, the differences could be due to chance. Additionally, the 11-year-old group also shows differences between infrequent and frequent enuresis, in the opposite direction. We have no adequate explanation for this; the large IQR shows that this could be due to chance too.

The paediatric ICCS definition is based on the relation between nocturnal urine production and bladder capacity. This relationship fits pathophysiologic reasoning (enuresis occurs when the amount of urine produced is too large for the bladder to store it), but does not resemble the actual amount of urine produced at night. We [11] and others [12] already suggested adjusting the NP definition in adults based on nocturnal urine production alone. Similarly, we suggest that for children, NP should also be defined based on nocturnal urine production alone, like others suggested as well [9]. Nevertheless, in our view, this should not necessarily be based on the 97.5 percentile in the normal population. In the end: although bladder capacity is important in enuresis, it does not belong to the definition of NP.

Small MVV

In our population, MVV without FMV increased with age, similar to previous research [2, 13]. Nevertheless, small MVV for age was present in 42% of men and 30% of women. This is in accordance with the literature [14]. Lack of inhibition of the micturition reflex is part of the aetiology as well [15]. In the older age groups, the proportion of patients with a small MVV is smaller and the proportion of NP (ICCS definition) is larger than in the younger age groups. This seems counterintuitive, as older enuresis patients are known to more often have non-monosymptomatic enuresis (NMNE) with daytime LUTS, often including urgency and frequency. In that case, a small MVV could be more frequently found. However, in our population, a high proportion of NMNE was found (81%), not differing over the age groups. Additionally, the definition of small MVV relies on the definition of EBC, which is defined for 4-12 year old children. From 12 years onwards, it is steady at 390 ml.
Difference between the sexes was mainly present in the age groups of 12-15 and 16-17 years in our population. Possibly, this could be explained by existing differences in (pre)pubertal developmental stages (Tanner stage) between males and females, influenced by hormonal changes. Additionally, other factors that could be taken into account are length and body weight. Due to the retrospective nature of the current study, these data were unfortunately not available.

Reference values and age differences

We showed that most parameters, like MVV, AVV and FMV, were positively influenced by age, as expected. Gender differences were not uniformly distributed over the age groups considering the different parameters assessed. As discussed, gender difference was present for specific age groups for small MVV. Koff presented his formula of bladder capacity in children ((age in years +2), in ounces) based on 35 non-enuretic children investigated by cystometry during anesthesia for urologic surgery like hypospadias repair. Bladder capacity was determined to be the volume above which the slope of the cystometric curve suddenly changed and pressure increased. Koff validated his formula in Starfields data of 203 non-enuretic siblings of enuresis patients [16]. Here, the larger of two voids during the daytime was taken as the bladder capacity. The most widespread, adjusted formula giving MVV in milliliters ((age in years +1)*30) [17], for children aged 4-12, was found to be valid in a healthy Danish population when the FMV was disregarded. When including the FMV, this overestimated the value found by Koff's formula [9]. In hindsight, the initial formula was indeed based on data without FMV, as explained.

For calculation of the MVV during the day, we therefore excluded the FMV. We did investigate an

older, tertiary care enuresis population, which could differ on several parameters from the healthy population. We showed that, in all age groups, at least 50% of our patients did not reach the expected 390 ml, as can be explained by the known high prevalence of low bladder capacity in enuresis patients. Additionally, we performed the analyses by including the FMV. This showed a lower prevalence of small MVV in all age groups, although one third of the younger age groups and one sixth of the older age groups still had small MVV, even when including this FMV.

Although it was previously stated that omitting the FMV could be in favour when assessing enuresis patients who do not void large amounts early in the morning due to enuresis episodes [9], it seems strange that for defining the largest voided volume during a day, the actual void that is often largest has to be excluded. The use of a circular argument like this for a theoretical model to be true is at least curious, while the theory should support reality as opposed to the current situation. Notably, Koff's definition is based on a non-physiological condition of anesthesia. In daily clinical practice, the definition is challenged as well, as the large first void is often taken into account when evaluating effect of bladder training and other interventions. Possibly, another definition that does take the morning void into account, could be helpful. In any case, in our opinion, this issue needs to be further discussed and adapted in future guidelines.

Adolescence – transition period

The results of our study highlight the differences in the prevalence of NP when using definitions reflecting different methodologies, currently used in pediatric and adult urology. Overall, ICCS has defined NP based on both bladder capacity and night-time urine production. Calculation of age based bladder capacity has been suggested by Koff [8] and Hjälmås [18]. Rittig et al. recently that these age based volumes were only valid if FMV was excluded [9]. The ICS-definition on the other hand focuses on the fraction of 24-hour urine produced during night-time. Physiology changes with ageing, which results in a proportional production of urine during all 24 hours. Because of this, it is difficult to evaluate if and when the amount of urine produced at night-time is pathological. We showed that the two definitions conflict, both in adolescents and in young adults. In this transitional phase from childhood to adulthood, it is not clear which definition should be used.

Transition refers to the process of children becoming independent adolescents and adults and to the process of the movement of patients from pediatric to adult care [19]. It has been thoroughly investigated in other medical specialties [20-23], and recently in urologic patients [24]. In this transition period, an entity – in this case explanation for complaints - should not change according to very different definitions used. To improve and help the fruitful cooperation of pediatric and adult urologists, and the transition of the adolescent patient in particular, it would be helpful if definitions were concordant. The interaction between pediatric and adult urology has been described to be limited when concerning training, conferences and joint diagnostic and treatment algorithms [25]. Possibly, enuresis is not easily identified as a chronic disease, which, like Shrewsbury mentioned for obesity, probably reduces the likelihood of it being included in transition planning [19]. Still, as in other conditions perverting from childhood to adult life, patients with enuresis will have to be protected from falling into a void between. This stresses

the importance of looking deeper into the process of transition in different urological diseases. We would like to encourage the development of an unambiguous definition of nocturnal polyuria to use both in paediatric and adult urology. In our opinion, both continence societies should discuss and supervise this process, similar to the nephrology societies that published a consensus statement concerning the transition from pediatric to adult renal services [26]. Overall, our findings do point out the importance of developing a solution for the transition from childhood to adulthood.

Limitations

Patients that filled in an FVC and were included in the descriptive analyses of the FVC variables were significantly older than those that didn't and were excluded. This could possibly be explained by the fact that older adolescents and adults are more dedicated to stop their enuresis, and thus will fill out the FVC more precisely. As we have presented reference values for different age groups, and missing data are not likely to be associated with this outcome, we believe that the incompleteness of data in the younger age group doesn't hamper the interpretation of these values.

The used FVC in itself could be seen as a limitation as well. It did consist of a three-day registration of both intake and output. However, the instructions on the form were not clear cut considering the nocturnal urine production, because no sleep and waking times were registered. We have ultimately tried to minimize influence of this problem by careful selection of the FVCs that were filled in correctly. The retrospective design of our study impairs the possibility to correct this. Another possible limitation of this study is that it concerns a highly selected population in a secondary/ tertiary care setting. This made it feasible to examine such a large group of patients with enuresis of this age, although the extrapolation potential could be limited for all enuresis patients aged 11 years and older.

Conclusions

Both small MVV and NP were found frequently in our adolescent and adult enuresis patients, which is in line with the current thought on causal factors. NP prevalence is quite different when using ICS or ICCS definitions, respectively. We would like to encourage the development of an unambiguous definition of nocturnal polyuria to use both in paediatric and adult urology.

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CHAPTER 5

Moderate agreement between bladder capacity assessed by Frequency Volume Charts and uroflowmetry, in adolescent and adult enuresis patients

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Abstract

Aims

Frequency Volume Charts (FVC) are recommended for the evaluation of enuretic patients. Although this is a good instrument for the assessment of functional bladder capacity, it is known that patient compliance could introduce problems. Therefore, we assessed whether uroflowmetry and post-void residual volume could replace FVC recordings in specific cases, by comparing the bladder capacity as measured by FVC or uroflowmetry.

Methods

We performed post-hoc analyses using data from a retrospective cohort study, in secondary/tertiary care. This included 907 patients between 2003 and 2013, aged ≥11 years, suffering from enuresis (≥1 wet night/fortnight). Data were collected from the medical files. Bland Altman plots were made to compare the two methods.

Results

Agreement between uroflowmetry and FVC was reasonable only when uroflowmetry was between 200 and 450 ml.

Conclusions

For individual clinical purposes, uroflowmetry can be used if values are in this range. For future research, we recommend to keep measuring bladder capacity with an FVC.

Introduction

To assess Lower Urinary Tract Symptoms, Frequency Volume Charts (FVC) are mandatory, both in children [1] and in adults [2]. In specific, functional bladder capacity (FBC) is estimated by means of maximum voided volume (MVV) in the FVC. This is defined as the largest single voided volume, excluding the first morning void (FMV) [1]. The advocated FVC length is 3 days, at the optimal balance between compliance (73%) and reliability (80%) [3]. Although EAU guidelines for male LUTS do not mention the FVC for measuring FBC [4], the pediatric EAU guideline does state that a voiding diary is mandatory for assessing voiding frequency and drinking habits [1; 5].In daily clinical practice, FVCs provide clinicians with a feasible, non-invasive method of FBC assessment. Patient compliance may however be problematic. As reliable information on the FBC is needed to make treatment choices, we wondered if this could be overcome by assessing the FBC by means of uroflowmetry - already performed to gain information on anatomical and functional abnormalities. Therefore, we investigated the agreement between FBC as measured by FVC and by uroflowmetry.

Methods

We performed post-hoc analyses on data from a retrospective cohort study in 907 consecutive enuresis patients, median age 14.8 years, treated with adapted dry bed training (DBT) during 2003-2013 in a specialized incontinence center. The data were manually collected from the medical files and entered in a database (Research Manager®). All patients filled in a 3-day FVC, and underwent three uroflowmetries followed by abdominal ultrasound to measure post voiding residual (PVR) volume, before DBT started. We selected the largest uroflowmetry void for analyses. Descriptions of DBT, data-collection, baseline characteristics and reference values for FVCs and uroflowmetry have been published in detail [6; 7]; 34% females, 65% primary enuresis, 81% non-monosymptomatic enuresis and 46% frequent enuresis (≥4 wet nights/week).

In the current analyses, we included 502 patients with available FVCs (with ≥2 voids and no missing voiding times), and voided volume of uroflowmetry and PVR. Excluded patients had a significantly lower average initial degree of enuresis (7.8±5.4 vs 8.9±4.1 wet nights/fortnight), and were significantly younger (13.8±4.3 vs 14.9±4.9 years) than included patients. Gender was not significantly different.

Definitions

MBV_{flow}: Maximum Bladder Volume, as measured by adding voided volume of uroflowmetry and PVR. MVV_{fvc}: Maximum Voided Volume, largest micturition excluding the FMV, as measured by FVC.

Results

We created Bland-Altman plots to compare MBV_{flow} and MVV_{fvc}. In these plots, the relation between MBV_{flow}, and the difference between MBV_{flow} and MVV_{fvc} are graphically depicted (Figure). Mean difference was-54 ml (SD 150), meaning that MVV was on average 54 ml larger on FVC-measurement

than during uroflowmetry. The trend-line has a positive slope, showing a positive relation between increasing MBV_{flow} and difference between MBV_{flow} and MVV_{fvc}. This was similar in all age groups.

Discussion

Comparison of uroflowmetry and FVC for assessing bladder capacity.

We evaluated the agreement between FVC and uroflowmetry for assessing bladder capacity and identified three different groups: MBV_{flow} <200 ml, 200-450 ml and >450 ml. It appeared that for MBV_{flow} <200 ml, MVV_{fvc} was structurally larger than MBV_{flow}. In our adolescent and young adult population, PVR was small or non-existent. In older, male populations, PVR could be larger, possibly resulting in a greater influence on the MBV_{flow}. Mainly for those uroflowmetries registering a capacity of 150 ml and less, or less than 50% of Expected Bladder Capacity (EBC) [4], current clinical practice is to redo the examination, as this is thought to be no valid observation. Although all patients underwent several uroflowmetries, and the largest voided volume was used for the analysis, several patients had a capacity of less than 100 ml. An explanation could be that, due to stress before the appointment, patients did not hold their urine accurately. The two measurement methods corresponded quite accurately in the MBV_{flow} 200-450 ml range. For patients with a capacity of 450 ml or more at uroflowmetry, however, MVV_{fvc} was lower than MBV_{flow}. One possible explanation is that some patients will hold their urine longer than they normally do when a uroflowmetry has to be performed. There may be a delay between the time patients would actually have gone to the toilet at liberty compared with when they're given access in the flow rate clinic. Another possible explanation is that larger bladders void less efficiently, resulting in a greater influence of PVR which is included in MBV_{flow}, but not in MVV_{fvc}.

The FVC represents (although not completely) the normal daily home situation, in contrast to uroflowmetry, which is performed in the hospital setting. Therefore, MVV_{fvc} most probably represents the normal situation more adequately. Advantages of uroflowmetry is that it is quick and easy and it takes even less time to interpret and administrate than the FVC. Disadvantages are costs for equipment and nurses, while FVC is free of charge. For both FVC and uroflowmetry, patient compliance is needed, for filling out the FVC or coming with a full bladder. In daily practice, information from both methods determines therapy.

Definition of bladder capacity/MVV

The first morning void will barely ever be registered during uroflowmetry. We compared the MBV_{flow} with the MVV_{fvc}, excluding the FMV, in line with current guidelines. Recently, it was found that if the FMV is taken into account, MVV does not equal the formula for EBC, whereas it does if the FMV is excluded [8]. EBC is defined as (age in years +1)*30, in ml for children aged 4-12 years [9].

However, the bladder is able to accommodate this FMV. In daily practice, it is a commonly expressed thought that the actual bladder capacity consequently will be larger. Especially for children suffering from enuresis, this is important, as a large FMV shows that the storage capacity of the bladder is sufficient and other causes should be evaluated. In the current time-frame in which other definitions are being reassessed, this issue should be evaluated as well.

Other measurement methods for bladder capacity

Previously, bladder capacity has been measured by other methods than the FVC, like cystometry or cystoscopy [9-11]. Measurement by cystometry under general anesthesia [9; 11] could overestimate the actual FBC, due to the influence of anesthetics on bladder behavior and the absence of reacting and waking to bladder stimuli. Cystometry without anesthesia showed a significant correspondence of cystometric capacity minus residual volume with MVV on FVCs [10]. Considering bladder capacity, FVC and uroflowmetry measurement were not compared before, as far as we are aware. As treatment choices are based on MVV/FBC, therefore, reliability of measurement methods is important.

Conclusion

In conclusion: FVC and uroflowmetry, used as measurement methods for assessing bladder capacity correspond accurately when capacity, measured by uroflowmetry, is between 200 and 450 ml. Therefore, for clinical practice, uroflowmetry volumes in that range can be used for treatment decisions, as the deviation will probably not result in an aberrant treatment. For future research, we recommend to keep measuring bladder capacity with an FVC, as in this instance, more reliable measurements are needed.

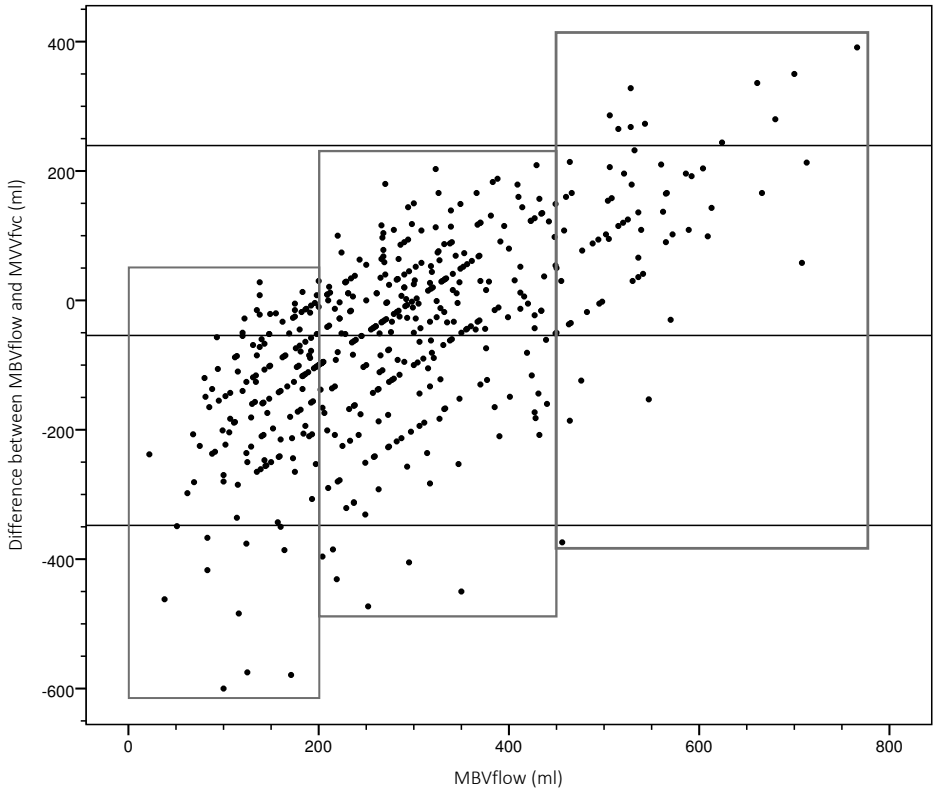

Figure 1. Bland-Altman plot comparing bladder capacity as measured by uroflowmetry and frequency volume chart.
N=502. Difference is measured by subtracting MBVflow from MVVfvc and expressed in milliliters.
MBVflow: Maximum Bladder Volume, as measured by adding voided volume of uroflowmetry and post-void residual volume. MVVfvc: Maximum Voided Volume, largest micturition excluding the first morning void, measured by frequency volume chart.

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PART II

Enuresis, nocturnal polyuria and functional bladder capacity: focus on definitions

CHAPTER 6

Positive short-term effect of adapted dry bed training in adolescents and young adults with treatment-resistant enuresis

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Submitted

Abstract

Introduction

Two percent of adolescents and adults suffer from therapy-resistant enuresis with considerable negative impact on self-esteem and relationships. We investigated the effect of Adapted Dry Bed Training (Adapted DBT) in previously treatment-resistant adolescents with enuresis.

Methods

Retrospective cohort study in 907 patients, treated between January 2003 and July 2013 by our Adapted DBT: a 5-days/4-nights in-hospital group-training consisting of enuresis-anamnesis, explanation, alarm treatment, day-time activities with the purpose of increasing self-esteem and group contact. Structured follow-up was performed by telephone. Data were collected from medical files. At 6 weeks, 3 and 6 months success of treatment was determined using ICCS-definitions. Secondary measurements included medication use after treatment. Sensitivity analyses were performed to control for missing values. Assumption worst-case/best-case scenario: patients with missing values had no response/ full response.

Results

Patients were aged 11–42 years (med 15, Inter Quartile Range 3.5), 34% female. At baseline, 81% had non-monosymptomatic, 65% primary, and 46% frequent enuresis. After 6 weeks, 46% ($CI_{95\%}$ 43-50) and 41% of patients had a full or partial response, respectively. After 6 months this accounted for 68% ($CI_{95\%}$ 65-72) and 25%. Sensitivity analyses showed that full responses ranged between 31% and 64% after six weeks and 43-80% after six months. Limitations are the retrospective study design and the amount of missing values. The scarce data on short-term follow-up are in line with our results, although different treatment outcomes were used. Additionally, our population was older.

Conclusions

Adapted DBT showed a positive response on short term, in adolescents and adults with therapy-resistant enuresis. Nevertheless, 32% of patients still had enuresis, indicating the persisting nature of the disorder.

Introduction

Enuresis, or discrete episodes of incontinence while asleep, has a negative impact on a child's self-esteem, relationships and school performance [1-3]. In a Dutch study, 0.5-2% of adults experienced enuresis [4], in comparison to 6% of children between 5-15 years of age [5].

Various treatment options are available for enuresis, like urotherapy, simple and complex behavioral therapy including alarm therapy or dry bed training, and drug therapy with desmopressin or anticholinergics [5-7]. Studies on treatment outcome mainly focused on young children, and were performed in small groups [5]. Data on treatment of adolescents or young adults is scarce.
Two studies concerning modifications to dry bed training on an outpatient basis in treatment resistant children and adolescents (mean age 11 years), showed success rates at six months in 55% and 87% of patients [8, 9]. Patients who remain wet when growing older, had more severe complaints. Yeung et al. found that both depression scores and sleep disturbances were significantly higher in patients than in controls [10]. Furthermore, a substantial proportion of patients with enuresis felt that the bedwetting had a significant adverse effect on their social life and career [11].

Guidelines for the assessment and treatment of enuresis are available in the Netherlands and in line with ICCS recommendations [12-14]. Nevertheless, for adolescents and young adults with therapy-resistant enuresis adequate treatment was missing. A specialized facility center (the Dry Bed Center-DBC) was initiated in 2003 by a collaboration of a continence nurse, urologist and the Dutch enuresis patient association. For patients who remained wet after regular outpatient treatment, an Adapted Dry Bed Training (Adapted DBT) was developed.
In this study we retrospectively evaluated the effects of this training program in adolescents and young adults with therapy-resistant enuresis.

Methods

A descriptive, retrospective cohort study was performed, based on chart data from consecutive patients treated with Adapted DBT between January 2003 and July 2013 in our center. In the Dry Bed Center, all referred patients suffering from enuresis were structurally evaluated at initial consultation. This consisted of two self-designed questionnaires concerning voiding complaints, a short psychological screening, medical history taking, physical examination, frequency volume chart (FVC) and uroflowmetry (MMS FlowMaster®) with post void residual (PVR) volume. If present, urological problems were treated before the training was started. We pursued to give all participants basic education on the anatomy and function of the urinary tract as well as lifestyle advices. Therefore, all participants (including MNE) received standard urotherapy, as described by Austin et al. [1] before being enrolled in the Adapted DBT. On an outpatient basis, anticholinergics were started if age-dependent small bladder capacity was present, or nocturnal bladder overactivity was suspected. Urodynamics were not routinely performed.

Inclusion criteria for Adapted DBT were a maximum voided volume of ≥300 ml, age ≥11 years and enuresis despite earlier standard therapies like desmopressin, alarm-, urotherapy, anticholinergic

drug therapy, or combination therapy if indicated. Some patients were dry while using desmopressin but repeatedly did not succeed in staying dry after cessation. These patients were enrolled in Adapted DBT for they wanted to be dry without using medication.

Adapted DBT program

The Adapted DBT is described in Appendix A. In short, it consisted of a 5-days/4-nights in-hospital group-training consisting of enuresis-anamnesis, explanation, use of a book as a diary [15], alarm treatment and day-time activities with the purpose of increasing self-esteem. Structured follow-up was performed by telephone.

Data collection

All medical files of patients treated at the DBC were collected from the hospital registry. Files were manually searched for baseline characteristics and outcomes. Ten percent of all files were subtracted in duplicate to check for possible errors. All data were entered in a database (Research Manager®). This included initial amount of wet nights, family history for enuresis, comorbidities, earlier treatments, constipation, maximal flow rate (Qmax) and PVR and medication use. Follow up data consisted of the amount of wet nights after Adapted DBT, medication use, alarm-therapy use and eventual other treatments. If at least one of two questions concerning Lower Urinary Tract Symptoms in the initial questionnaire was positive, we categorized patients as having NMNE.

Outcome parameters

We defined primary treatment outcome according to current ICCS recommendations [1], based on the percentage decrease of number of wet nights compared to baseline symptoms. The ICCS defined 'initial success' as: no-response: <50% reduction, partial response: 50-99% reduction, complete response: 100% reduction[1]. Secondary measurements included the use of pharmacological therapy for enuresis during follow-up. To compute these response groups, both number of wet nights before Adapted DBT and outcome are needed. Alternatively, treatment effect can be expressed as complete if patients are dry after treatment – irrespective of pre-treatment severity. For this, only post-treatment severity is needed. We performed analyses, both according to the ICCS methodology, as well as to the alternative method.

Statistical analysis

Effect of treatment during follow-up was analyzed for different subgroups. Age distribution is presented as median and Inter-Quartile-Range (IQR) due to non-normal distribution of the data.
We categorized the patients in two age groups, adolescents: 11-17 years old, and adults: 18-42 years old. Degree of enuresis was categorized as frequent (≥ 4 days/week) or infrequent (<4 days/week) [1]. Because of the high number of missing values during follow-up, a sensitivity analysis was performed, presenting a worst and a best-case scenario. The following assumptions were made: worst-case scenario: all patients with missing values had no response to treatment, best-case scenario: all patients with missing values had a full response to treatment.

Those patients that were in follow up after six weeks, were assessed after six months for missing value pattern, to examine whether the best or worst-case scenario of response is most likely.

Differences in treatment outcome for gender, age and degree of enuresis were tested using two-sided Chi Square test. We considered a p-value of ≤.05 as statistically significant and analyzed all data using IBM SPSS Statistics version 22.

Results

Patient characteristics

In this study we enrolled 907 patients, aged 11–42 years (median 15, IQR 3.5) (Table 1). Of these, 866 patients followed the regular Adapted DBT, and 41 the Adapted DBT 'plus-group'. Eleven

	% (N)	Median	IQR [Q1-Q3]
Age, years		14.8	3.5 [13.4-16.9]
11 – 17	81 (733)		
18- 42	19 (174)		
Gender			
Male	66 (601)		
Female	34 (306)		
Baseline wet nights per week		4.5	3.5 [2.5-6]
Mild (0-3)	33 (300)		
Severe (4-7)	46 (418)		
Missing information	21 (189)		
Type of enuresis			
MNE	11 (98)		
NMNE	81 (735)		
Missing information	8 (74)		
Specific questions for NMNE			
Urinary leakage during day	29 (262)		
Holding urine easily during day	65 (587)		
Primary/secondary enuresis			
Primary	65 (593)		
Secondary	17 (153)		
Missing information	18 (161)		
Family history of enuresis			
Yes	61 (550)		
No	30 (276)		
Missing	9 (81)		
AD(H)D, ASD	11 (101)		
Earlier treatments*			
Lifting	67 (608)		
Regular alarm clock	58 (528)		
Alarm training	92 (834)		
Desmopressin	83 (755)		
Anticholinergics (Solifenacin, Tolterodin, Oxybutinin)	16 (143)		
Imipramin	4 (37)		
Qmax (ml/sec) at initial visit		30	16 [23-39]
PVR (ml) at inital visit		0	10 [0-10]
Times pt underwent Adapted DBT			
Once	(896)		
Twice	(11)		

Table 1. Patient characteristics at baseline. N=907
#Combination of treatment options was possible. Abbreviations: AD(H)D: Attention Deficit (Hyperactivity) Disorder. ASD: Autism Spectrum Disorder. IQR: Inter Quartile Range. Adapted DBT: Adapted Dry Bed Training. NMNE: Non Monosymptomatic Nocturnal Enuresis. PVR: Post Void Residue. Qmax: maximal voided stream in ml/sec

	6 weeks, % (n)				*3 months, % (n)*				*6 months, % (n)*			
Response category (ICCS)	No	Partial	Full	N	No	Partial	Full	N	No	Partial	Full	N
Worst case scenario	42 (381)	27 (249)	31 (277)	907	42 (384)	21 (194)	36 (329)	907	42 (378)	16 (141)	43 (388)	907
Available data	**13 (76)**	**41 (249)**	**46 (277)**	**602**	**11 (67)**	**33 (194)**	**56 (329)**	**590**	**7 (39)**	**25 (141)**	**68 (388)**	**568**
Best case scenario	8 (76)	27 (249)	64 (582)	907	7 (67)	21 (194)	71 (646)	907	4 (39)	16 (141)	80 (727)	907

	No	Partial	Full	P	No	Partial	Full	P	No	Partial	Full	P
Age, years				0.312				0.043				0.213
11 – 17	12 (61)	43 (215)	45 (228)		11 (54)	35 (173)	54 (267)		7 (33)	26 (127)	67 (326)	
18- 42	15 (15)	35 (34)	50 (49)		14 (13)	22 (21)	65 (62)		7 (6)	17 (14)	76 (62)	
Gender				0.003				<0.001				0.044
Male	14 (56)	45 (175)	41 (161)		13 (50)	38 (149)	49 (193)		8 (31)	27 (102)	65 (248)	
Female	10 (20)	35 (74)	55 (116)		9 (17)	23 (45)	69 (136)		4 (8)	21 (39)	75 (140)	
Baseline wet nights per week				<0.001				0.009				0.210
Mild (0-3)	18 (45)	32 (82)	50 (127)		15 (35)	26 (64)	59 (143)		8 (18)	21 (50)	71 (169)	
Severe (4-7)	9 (31)	48 (167)	43 (150)		9 (32)	37 (130)	53 (186)		6 (21)	28 (91)	66 (219)	

	6 weeks, % (95%CI, n)		*3 months, % (95%CI, n)*		*6 months, % (95%CI, n)*	
Post treatment status	Wet	Dry	Wet	Dry	Wet	Dry
irrespective of pre-treatment	54	46	45	55	32	68
severity	(50-57, 416)	(43-50, 360)	(41-48, 339)	(52-59, 419)	(28-35, 227)	(65-72, 491)

Table 2. Treatment results after 6 weekss, 3 and 6 months, including sensitivity analysis N=907.
P-values derived from Pearson Chi-square testing. P<0.05 is considered significant. CI: Confidence interval.
Assumption worst-case scenario: all patients with missing values had no response to treatment.
Assumption best-case scenario: all patients with missing values had a full response to treatment.

Figure 1. Treatment results after 6 weeks and 6 months, including sensitivity analysis
Assumption worst-case scenario: all patients with missing values had no response to treatment.
Assumption best-case scenario: all patients with missing values had a full response to treatment.
Response groups according to International Children's Continence Society criteria.

patients underwent Adapted DBT twice due to inadequate response to the first treatment and are consequently described twice.

At baseline, 81% had NMNE, 65% had primary enuresis. 46% had frequent enuresis. All patients underwent several treatments in the past (Table 1). Twenty-four percent of the patients were using anticholinergics before and during the Adapted DBT.

Results of treatment

ICCS-response categories could be estimated for 602 (66%), 590 (65%), and 568 (63%) patients after six weeks, three and six months, respectively. We encountered 85% missing values for the 1-year follow up. Therefore, these results are not presented.

The amount of full response increased over time, from 46% to 56% and 68%, after six weeks, three and six months, respectively. Partial response was shown in 41%, 33% and 25%, respectively. According to the post-treatment analyses, 46% ($CI_{95\%}$ 43-50), 55% ($CI_{95\%}$ 52-59) and 68% ($CI_{95\%}$ 65-72) of the participants were dry after six weeks, three and six months, respectively (Table 2, Figure 1).

Sensitivity analyses showed that full responses ranged between 31% and 64% after six weeks. For three and six months these ranges were 36-71% and 43-80% respectively. Missing values after six months were encountered in all three six-week response groups. The no response group at six weeks had a higher percentage of missing values after six months. This indicates that the true treatment effect will be in the direction of the worst-case scenario.

Subgroup analyses for the different time frames are presented in Table 2. Adults had a significantly different response after three months compared to adolescents; in the other time frames, no

significant differences were found. In contrast, gender was found to be associated with significant different responses: fewer males had a full response than females in all time frames. Significantly more mild-enuresis patients had a full response in all time frames than severe enuresis patients, although it is questionable whether this difference is clinically meaningful. The normal and 'plus-group' did not significantly differ in baseline severity of complaints, response or distribution of the response over the different response subgroups (data not shown).

Medication use/other treatments
During the last outpatient clinic contact before the Adapted DBT, 60% of patients used medication (44% desmopressin, which was stopped before Adapted DBT as part of the training program). After six months, 3% of patients had restarted desmopressin and 5% used anticholinergics. During follow up, 13 patients underwent one or more additional treatments, like laxatives, diuretics, alternative medicine, Botulinum toxin, psychotherapy, or additional urological investigations.

Discussion

In this retrospective study, an intensive training program appeared to be successful in the majority of adolescent and adult patients with enuresis, even when failing prior therapy. Despite this positive effect, about one third of patients still suffered from enuresis of some degree 6 months after the Adapted DBT. This emphasizes the possible persistence of the problem. We believe that this is the largest cohort study describing the effect of intensive training for enuresis in adolescents and young adults.

We aimed to describe the effect of treatment up to one year after Adapted DBT. We encountered many missing values at this one-year follow-up. This may be due because there was no actual treatment-relationship with our clinic anymore. We therefore had to restrict our conclusions to a shorter period of six months. Due to the retrospective nature of our study, this could not be influenced. The ICCS currently defines complete success as having no relapse two years after treatment [1]. We are unaware of any publication for this duration of follow-up. The scarce data on short-term follow-up are in line with our results, although different treatment outcomes were used. Full response of 55% (n=49) [8] and 87% (n=52) [9] at six months was shown in two small outpatient studies on dry bed training. Both included younger patients, aged 7-23 (mean 11) and 4-20 (mean 10) years, respectively. The treatment effect of 68% after six months in our study is probably an overestimation, due to the large loss to follow up in the six-week-non-response group.

To be enrolled in the Adapted DBT, persisting enuresis after other unsuccessful treatments was required. Although our patients all sought medical attention, this could represent only a small group of all adolescent enuresis patients. In a tertiary enuresis clinic in Hong Kong, 37% of primary enuresis patients had never sought medical attention nor received therapy in the past [16], alike to the 20% of the Italian population of adolescents who were referred to specialists in secondary care [17].

Between 10 and 19 years of age, an annual spontaneous cure rate of 16% is described [18]. However, for patients having been exposed to other therapies already, such spontaneous cure rates

are unknown. We do not expect that natural improvement has had a significant influence on the described response rates at 6 months in our study population. We do acknowledge that the lack of a control group limits the possibility to make firm conclusions on the efficacy of Adapted DBT.

In general, adolescents show a low motivation for treatment compliance [17]. However, in our study, patients were motivated to follow the Adapted DBT. In follow-up we experienced many missing values. First of all, this may be due to the retrospective character of our study. For some patients, the long term response was described in the medical chart as "improved/going better", but not described in actual amount of dry and wet nights.

Additionally, the amount of missing values may be explained by the fact that patients, after having been treated, have no interest in follow-up. Possibly, the best conclusion is that enuresis is a difficult disease to gather long term results, as was illustrated by the low response rates in other long term questionnaire studies [19]. In general, non-adherence is a major problem in all long-term therapies [20].
Of our patients, 46% suffered from severe enuresis, reflecting the nature of our secondary/ tertiary care center. Yeung et al. [10] suggested, based on their epidemiological study in the general population of Hong Kong, that children suffering from more severe symptoms might have a significantly higher chance that the enuresis persists into adulthood, representing a more pronounced form of the condition [10]. Nevertheless, more than half of our patient group had mild complaints. The fact that they applied for medical care indicates that complaints of mild enuresis can persist over time. Due to the uncertainty of having a wet or a dry night, mild enuresis patients have to take precautions every night, like desmopressin or diaper use. In our population, adults had a significantly different response after three months compared to adolescents; in the other time frames, no significant differences were found. We feel that this initial and fading difference could maybe due to reasons of motivation depending on age.
The main changes of our modification to the classical dry bed training were that we performed the Adapted DBT in an age-matched group of participants, clinically during 5 days/4 nights with a bedwetting alarm. Neveus [21] described that new alarm treatment attempts can work in children, even if this was not successful two years before [21]. The social stigma associated with enuresis [10] and the fact that only 2% of adolescents and young adults suffers from persisting enuresis, results in patients being unaware of other patients. Group contact stimulates interaction and recognition by sharing emotions and obstacles in daily life, and patients can motivate and support one another [22-24]. The multidisciplinary approach implied both nursing interventions and reinforcement of self-esteem.

Eighty-one percent of our patients had NMNE. In other populations with persisting enuresis, high incidences of NMNE [11], as well as high incidences of detrusor overactivity and bladder outlet obstruction on urodynamics are described [16, 25]. This emphasizes the importance of a careful diagnostic work-up in this group [8, 21].

Children with enuresis show clinically relevant behavioral problems at rates two to four times higher than non-bedwetting children [26]. The most common co-morbid behavioral disorder in enuresis is

ADHD. In our center we experienced that children with ADHD and ASD needed more attention and smaller groups. In 2011 we started with 'plus-groups'. As the normal and plus-groups did not differ in baseline enuresis severity or treatment outcome, we decided to describe them in the overall group. At start of the Adapted DBT 24% of the patients used anticholinergics, decreasing to 5% at six months, which is comparable to literature [8]. This could indicate that additional training can help overcome small bladder capacity or even night-time detrusor overactivity, decreasing drug use and preventing possible side effects. A small group (3%) had restarted the use of desmopressin at six months.

Conclusions

Our data suggest that older patients (adolescents and young adults), even those who have failed prior therapy, seem to have a significant clinical response on the short term to Adapted DBT, with a full response in 68% of all patients at 6 months. Despite the positive effect of Adapted DBT, 32% of patients still had enuresis, indicating the persisting nature of the disorder.

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CHAPTER 7

Predictors for a positive outcome of adapted clinical dry bed training in adolescents and adults with enuresis

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Abstract

Introduction

Adapted Dry Bed Training (Adapted DBT) has been shown to be effective in therapy-resistant adolescents and adults with enuresis. Given the substantial impact of enuresis and time-consuming character of MDBT, we investigated which patients benefited most from MDBT. Therefore, we identified predictors for a successful treatment response to MDBT in this population.

Methods

Retrospective cohort study in 907 consecutive patients, aged 11-42 years, subjected to in-hospital Adapted DBT in our Dry Bed Center between January 2003 and July 2013. Outcome was defined as treatment success after six months (primary outcome) and six weeks. Results of logistic regression analyses are presented in odds ratios and 95% confidence intervals.

Results

Predictors for a successful treatment response to Adapted DBT in adolescents and adults with enuresis after six months are gender (female), initial degree of enuresis (mild: 0-3 nights/week), current diaper use, never used anticholinergics in the past and degree of enuresis six weeks after training. Predictors for successful treatment response after six weeks are only gender and initial degree of enuresis. Limitation is the low explained variance of our model, showing that many other factors, not included in our study, could be of interest in the prediction of success.

Conclusions

Several factors that predicted a successful treatment response of Adapted DBT after six weeks and six months were identified. However, the low explained variance of our model suggests that other non-identified factors are also important in predicting outcome.

Introduction

Enuresis negatively affects the health related quality of life of patients and parents [1] and is associated with a lower self-esteem [2]. In adolescents and adults, it can cause stress and social problems [3], having more impact on self-esteem and quality of life than in younger children [4].
Treatment options for enuresis have been investigated mainly in children. Alarm treatment and desmopressin are both first-line treatments [5]. Only 18-38% of patients remain dry after discontinuing desmopressin [6], although alarm therapy also has a relapse rate of 50% [7]. There is some evidence that the relapse rate is lower when combining alarm therapy and dry bed training. Classical dry bed training consists of a clinical training night, waking every hour to go to the toilet, cleanliness training (changing the bed) and positive practice (patient practices getting up and going to the toilet several times) if the bed is wet [8].
Several authors slightly changed dry bed and alarm therapy and stated that adequate use of the alarm was essential to the success of treatment [9, 10]. A modified form of home-bound dry bed therapy (DBT-M) in 74 children, was as effective as alarm therapy alone [11]. Only a few studies reported predictive factors for success of enuresis treatment, but these results have so far not been replicated [12-15].

Adapted Dry Bed Training (Adapted DBT) in a specialized incontinence centre is effective in therapy-resistant adolescents and adults. Given the impact of enuresis as well as the intensity and time (and money)- consuming character of Adapted DBT, it is important to identify patients that benefit most of Adapted DBT. Therefore, in this study we aim to predict a successful treatment response to Adapted DBT in adolescents and adults.

Methods

Patient selection
We performed a retrospective cohort study on 907 consecutive patients to evaluate the characteristics of patients that were treated with Adapted DBT in our Dry Bed Center (DBC) between January 2003 and July 2013. Patients were adolescents and adults aged 11 to 42 years.

Treatment
The DBC is a secondary and tertiary care facility. At the initial visit to the DBC outpatient department, all new patients were asked to fill in a number of questionnaires, as well as a 3-day frequency volume chart. For the amount of wet nights, a chart was used which represented 14 nights, on which patients had to fill in whether they were wet or dry. Patients were evaluated by uroflowmetry and ultrasound for assessing the Post Voiding Residual volume (PVR). If no additional urological investigations were needed, advice was given or desmopressin, anticholinergic treatment or alarm training was started. If maximum voided volume of 300 ml was reached but enuresis was still present, patients were considered eligible for Adapted DBT. The actual Adapted DBT consisted of an in-hospital stay for 5 days (4 nights), in a group with other patients of similar age. During the first training night, patients were woken every hour to drink a glass

of water and go to the toilet. During the following nights, patients slept with an alarm (Contessa ®, Urifoon B.V., Amstelhoek, the Netherlands) and they were instructed to set a personal alarm clock at an individually adequate moment during night-time to try to prevent wet nights. If a patient was wet, the attending social-pedagogic worker got a signal and could see whether or not the patient acted right (cleanliness training). Daytime activities included exercises to increase self-confidence. After the in-hospital stay, patients used their bed-wetting alarms and personal alarm clocks at home. They were regularly followed up by telephone by social-pedagogic workers weekly for the first six weeks, followed by monthly contact until six months.

Data collection

All medical files of patients treated at the DBC were collected from the hospital registry. Files were manually searched for baseline characteristics and outcomes. Data was separately extracted in duplicate from 10% of all files. All data were entered in a database (Research Manager ®, Cloud9 Health Solutions, Deventer, the Netherlands). If at least one of two questions concerning LUTS (any urinary leakage or inability to hold urine easily during the day) at the initial questionnaire was answered positive, patients were diagnosed having non-monosymptomatic enuresis. When uroflowmetry was performed more than once at the initial visit to the outpatient clinic – two to three times, as Dutch guidelines advise [16]-, the uroflowmetry with the largest volume was used. We categorized the degree of enuresis at initial visit to the outpatient clinic as mild (0-3 wet nights per week) and severe (4-7 wet nights per week), according to current International Children's Continence Society (ICCS) guidelines (in-frequent 0-3/wk and frequent 4-7/wk) [17].

Outcome parameters

The primary outcome parameter was treatment success six months after training, as long-term effects are of primary interest. The secondary outcome parameter was treatment success six weeks after training. The patients were distributed in two categories: responders (dry) and non-responders (still wet), although the ICCS proposed recently to use other categories [17]. Main argument for this was our sense that patients are only really cured and satisfied with dryness. If patients are still sometimes wet they will always have to take precautions anyway, because in such cases, the moment of involuntary urine loss cannot be anticipated.

Statistical analysis

Causality is no issue in prediction models [18]. Therefore, all parameters available in our database were used as possible predictors. First, frequency tables of all variables were made. We found that up to 30% of data was missing. The data were missing at random, as tested by Little's MCAR test, which was significant. We therefore performed multiple imputations, using pooled data of 30 imputations [19], using the outcome parameter as the dependent variable in the imputation. This was performed in two separate databases for the primary and secondary outcome. For both outcomes, the following parameters were used for the imputation: gender, date of birth, earlier treatments, diaper use, family history, been dry in the past, constipation, year of treatment, character of voided stream (bell/tower/plateau shaped uroflowmetry curve), psychological features, sleeping problems, back problems (dimple, pain, deformities), degree of enuresis during intake (number of wet nights per fortnight) and age.

Secondly, we performed univariate analyses. For this we used univariate logistic regression between the outcome parameters and all individual explanatory variables. All explanatory parameters with a (chi-square) p-value of <0.25 were subsequently used in the correlation matrix, the other explanatory parameters were discarded from the subsequent analyses. Correlation matrices were checked for collinearity. As no variables had a collinearity > 0.8, no additional variables were discarded for the subsequent analysis [20].

For both outcomes, logistic regression models were run by using the hierarchic standard regression method ("Enter" method in SPSS) [21]. Treatment success was entered as dependent variable and possible predictors were entered as independent variables (see legend Table 2 and 3). Subsequently, a stepwise backward selection strategy was used, i.e. the model was run in steps after excluding the predictive parameter with the highest p-value in the last model, until the simplest model, only expressing significant predictors, was obtained.
Finally, the explained variance was expressed by Nagelkerkes R^2 and the model fit was evaluated by the Hosmer and Lemeshow goodness-of-fit test [22].

We present the results of the analysis in the original and pooled imputed data. The predictive capacity of the variables is expressed in odds ratios (OR) with 95% confidence intervals (CI). Reported p-values are two-sided and a p-value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 22).

Results

Patient characteristics
Baseline characteristics of the 907 patients are presented in Chapter 6.

	OR	CI 95%
Original data		
Gender (male vs female)	0.563	0.370- 0.856
Initial degree enuresis (mild vs severe)	1.701	1.086- 2.665
Diaper use (no vs yes)	0.542	0.354- 0.832
Anticholinergic in past (no vs yes)	4.083	1.341- 12.438
% wet nights at 6 wk	0.982	0.970- 0.993
Pooled imputed data		
Gender (male vs female)	0.628	0.429- 0.920
Initial degree enuresis (mild vs severe)	1.839	1.204- 2.808
Diaper use (no vs yes)	0.647	0.426- 0.982
Anticholinergic in past (no vs yes)	2.814	1.056- 7.500

Table 1. Results logistic regression analysis for primary outcome: success after six months
OR: odds ratio, CI: confidence interval
Independent variables with a p<0.25 in the univariate analyses included in the multivariable model were: gender, age (adolescent or adult), past treatments (taking up to go to toilet at night, desmopressin, anticholinergics), current diaper use, urgency, urinary tract infection in the past, family history positive of enuresis, (psychosocial) medical history, medication just before Adapted DBT, degree of enuresis before Adapted DBT, how often wet per night before Adapted DBT, degree of enuresis at six weeks, ever been dry, first or second time Adapted DBT, volume voided at uroflowmetry. Only the remaining variables are presented.

Primary outcome: response after six months

Data from 600 (65%) patients were available for the final logistic regression model in the original data six months after in-hospital training. Of those, 408 (68%) patients were dry. After multiple imputation, data from 758 (84%) patients were available for performing the final logistic regression model, of whom 502 (66%) were dry.

Gender ('female'), initial degree of enuresis ('mild'), diaper use at the intake ('yes'), and previous use of anticholinergics ('no') are the predictors of success after six months in our cohort (Table 1) in both the original and the pooled data. In the original data, an additional predictor was found: degree of enuresis after six weeks, although the added value was limited with an OR of 0.982. The Nagelkerke R^2 was 0.087 and 0.082 (original and imputed data). The Hosmer and Lemeshow goodness-of-fit test showed a non-significant value of 0.355 and 0.297 (original and imputed data) at the final step of our model, suggesting that the model fits to our data, especially when taking the high sample number into account. Nevertheless, the Nagelkerke R^2 shows that the model only explains a minor part of the outcome parameter.

Secondary outcome: response after six weeks

Data from 689 (76%) patients were available for the final logistic regression model in the original data at six week follow-up. Of those, 314 (46%) patients were dry. After multiple imputation, data from 809 (89%) patients were available for performing the final logistic regression model, of whom 362 (45%) were dry. Gender and initial degree of enuresis were the significant predictors of success after six weeks (Table 2), both in the original and the imputed data. In the latter data, men had an OR of 0.665 (95%CI 0.481-0.918) compared to women. Mild enuresis an OR of 1.460 (95%CI 1.061-2.009) compared to severe enuresis. The Nagelkerke R^2 was 0.023 and 0.025 (original and imputed data). The Hosmer and Lemeshow goodness-of-fit test showed a significant value of 0.005 and 0.014 (original and imputed data, respectively) at the final step of our model, suggesting that the model fits poorly to our data.

	OR	CI 95%
Original data		
Gender (male vs female)	0.676	0.493- 0.928
Initial degree enuresis (mild vs severe)	1.443	1.043- 1.996
Pooled imputed data		
Gender (male vs female)	0.665	0.481- 0.918
Initial degree enuresis (mild vs severe)	1.460	1.061- 2.009

Table 2. Results of logistic regression analysis for secondary outcome: success after six weeks
OR: odds ratio, CI: confidence interval
Independent variables with a p<0.25 in the univariate analyses included in the multivariable model were: gender, age (adolescent or adult), past treatments (taking up to go to toilet at night, alarm therapy, setting own alarm, medication, desmopressin, anticholinergics, imipramin), current diaper use, how wet if no use of diapers, how often wet per night, diurnal incontinence complaints, urinary tract infection in the past, pain during voiding, family history positive of enuresis, degree of enuresis before Adapted DBT, ever been dry (and during how many months)), own prediction (between 1-10) of success before Adapted DBT, type of group (normal or plus, with additional psychotherapy) referred by first or secondary care, volume voided at uroflowmetry. Only the remaining variables are presented.

Discussion

Factors that could predict successful treatment response of Adapted DBT in adolescents and adults with enuresis after six months are gender, initial degree of enuresis, current diaper use, never having used anticholinergics in the past and degree of enuresis six weeks after training. Factors that predict the outcome after six weeks are gender and initial degree of enuresis.

We were able to create a prediction model for those parameters that are easily available and relevant for predicting a successful treatment. Such parameters are of importance in daily practice as well as in the design of prospective (intervention) studies. Most adolescents and adults with enuresis already experienced many different therapies for which a strong motivation is essential. Predicting which patients will most likely benefit from therapy helps in several ways: informing patients on their possible individual benefit, more realistic goals, and selection of patients for specific therapies and directing treatment in a cost-effective way.

As far as we are aware, no prediction model for the effect of in-hospital dry bed training in combination with alarm therapy for enuresis has been published yet. However, Adapted DBT consists of several components, for which prediction models have been described in literature [11-13, 15], which are however limited due to lack of external validation. A multivariate analysis in a recent trial in primary MNE children treated by desmopressin or enuretic alarm for six months, showed that treatment group, monthly income and severe enuresis (>5 wet nights/week) were independent important predictive factors for cure after first line treatment [15]. Response categories were complete, good, partial and no response. Severe enuresis being a predictive factor for success is in contrast with our results. Behaviour therapy (charts, motivational therapy and bladder awareness training without alarm therapy) was analysed in a population of 122 (74 completed study) children aged 5-9 years old. Thickness of the bladder wall measured by ultrasound was strongly correlated to poorer treatment response and higher severity of the complaints [12]. This treatment differed to our Adapted DBT by it being on an outpatient basis, only focusing on behavioural therapy, not on alarm therapy. Response categories were the same as used by Onol et al. [15], suggested by the ICCS in 2006 [23]. Devlin et al. treated 127 patients aged 6-17 (mean 8.8) years with alarm therapy and outpatient behavioural therapy (cleanliness training, personal hygiene, daily bladder exercises and charts) [13]. Response was categorised in dry and still wet, as 'children who achieved >50% improvement in wetting but not full cure were considered to be failures'. Their prediction model showed that risk of failure was 5% at six months and 10% at 12 months if none of the following adverse variables was present, increasing by family stress and lack of child's distress (six months) and lack of child's distress, psychiatric disorder and developmental delay (12 months) [13].

Butler's DBT-M also took place on an outpatient basis, in 6.1-14.4 year olds. A predictive factor for treatment response was teasing by siblings, as reported by the child. Drop-out rate increased if maternal anger over their child's bedwetting was present [11]. Our Adapted DBT differs from Devlin and Butlers therapies by the treatment taking place in-hospital with special consideration to gaining self-confidence, and the alarm-therapy being continued for six weeks. Additionally, our population is much larger and concerns only adolescents and adults.

Recently, new ICCS guidelines have been published [17], proposing three instead of four response categories, as this was thought to be relevant for research purposes. The evidence base for this change remains unclear. As stated, throughout the years, different categories have been used. We argue that patients are only really cured with dryness, and therefore, we chose for two response categories: dry or wet.

We believe that our study has two main limitations. First, the number of missing data was considerable, due to the retrospective nature of our study. This could have led to attrition bias in our study. We aimed to improve the accuracy of our models by multiple imputing our data on the outcome parameters. We chose for presenting both models in the original as well as in the pooled imputed data, to give the reader insight in the possible difference. We have shown that neither the models nor the fit of them differed, except for the degree of enuresis at six weeks, which was found as additional predictor in the 6 month-original-data-model compared to the pooled model. This variable added only little to the model with a very small OR.
The second limitation of our study is that our models showed a low explained variance. We believe this might illustrate that our study population may have been more homogeneous than previously expected. This can also be explained by the multifactorial origin of enuresis, patients in different age groups, with a different medical history concerning enuresis treatments. The low R^2 of our model shows that many other factors, not included in our study, will be of interest in the prediction of success.

Although the urge arises to try to explain why the variables that we found predict success, we cannot infer any causal relationships based on (these) prediction models. One of the next steps should be to externally validate our prediction model because non-validated models should not yet be used in clinical practice, preferably using patients from another hospital [24].

Conclusions

Factors that could predict successful treatment response of Adapted DBT in adolescents and adults with enuresis after six months are gender (‘female’), initial degree of enuresis (‘mild’), current diaper use (‘yes’), anticholinergic drug use in the past (‘none’) and degree of enuresis six weeks after training. Factors that predict the outcome after six weeks are gender and initial degree of enuresis.

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CHAPTER 8

Difficulties in gathering long-term follow-up after treatment for enuresis: a cross-sectional questionnaire study

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Abstract

Introduction

Enuresis and nocturia share etiological factors, but little is known about their association. We aimed to study the presence of nocturia in patients formerly treated for enuresis, but experienced problems with response. We focus on this and on possible solutions for this field of research.

Methods

Cross-sectional questionnaire (ICIQ M/FLUTS and LUTSqol) study in 553 patients ≥18 years, treated between 2005-2011 by adapted Dry Bed Training. Invitations were sent in three, sequential, steps: initial invitation (9% response), subset called (15% response), random subset, n=50, offered reward (42% response). Due to these low response rates, we decided to focus on comparing patient characteristics according to the invitational phases, instead of comparing the prevalence of nocturia between initial success-of-treatment-groups.

Results

Of the 76 responders, median age was 23 [IQR 20-25], 41 were men. ICIQ and bother scores were all low. Nocturia (≥1x) was present in 55% (men) and 72% (women); clinically relevant nocturia (≥2x) in 8% (men) and 25% (women). Ten men (30%) and 9 women (28%) had enuresis (≥1/28 nights). In the different invitation phases, patient characteristics were not significantly different, although the reward-group had slightly lower bother scores and nocturia prevalence.

Conclusions

We faced serious problems in successful patient recruitment in studying long-term follow-up of adapted DBT for enuresis. As others have faced this as well, we doubt if long-term follow-up is feasible in this patient group. When gathering long-term follow-up in a retrospective study, we recommend to include a reward to increase response rates and thus interpretability of the results.

Introduction

Enuresis (the involuntary loss of urine at night) is common in children (15-20% of five year olds), and still exists in up to 2% of young adults [1, 2]. Those patients who remain wet if they grow older, have more severe complaints [3]. Nocturia represents the condition in which patients do arise in response to bladder stimuli. In adults, two or more nocturnal voidings are increasingly considered to be the threshold at which nocturia is more likely to be symptomatically bothersome [4].

Enuresis and nocturia share etiological factors such as nocturnal polyuria and a small bladder capacity. Still, little is known about the association between enuresis and nocturia. The available information is gathered from retrospective studies in former enuresis patients or their parents. The other way around; investigating past enuresis in older nocturia patients will lack information about the course of the enuresis. Mothers of children with enuresis who experienced enuresis in their own childhood, show a higher risk of having nocturia in adulthood [5]. Additionally, 35% of former – mainly non-monosymptomatic enuresis patients in a tertiary care population had (clinically relevant) nocturia. The response rate in this study was 41% [6]. The International Children's Continence Society states that long term follow up of enuresis of two years or more is necessary [7], but it seems to be very difficult to gather a high response rate and thus valid answers [8].
A detailed study on nocturia comparing groups of (former) enuresis patients could be of help in understanding the evolution of enuresis into nocturia. Especially differences in enuresis degree, and applied methods for the treatment of enuresis are of interest. Asides, the impact of nocturia on health related quality of life is of interest for clinical care of this patient group.

We aimed to study the presence of nocturia and other LUTS, and their impact on quality of life in patients formerly treated for therapy-resistant enuresis by adapted Dry Bed Training (DBT): long term follow up studied by cross-sectional questionnaires. Unfortunately, we experienced large difficulties regarding appropriate response rates. In this paper, we will focus on these problems and possible solutions for this field of research.

Methods

We performed a cross-sectional questionnaire study in which patients formerly treated by Adapted DBT in the Dry Bed and Pelvic Center (Droog Bed en Bekken Centrum – DBBC, Meppel, The Netherlands) were included. Results of the initial treatment of this group have been published previously [9].

Patient selection
We selected a group of patients treated between 2005 and 2011, and were 18 years or older at the moment the questionnaire was sent in July 2014. The study closed in August 2015. Hence, the time since treatment varied from 3 to 9 years. This period is chosen because the ICCS defines long term follow up being a follow up of two or more years after treatment [10].
Patients were selected from the hospital/outpatient department records at Diagnosis Treatment

Code (in Dutch "Diagnose Behandel Combinatie", DBC) and were contacted by postal mail using an explanatory letter. The questionnaires could be filled in digitally or on paper, according to the patient's wishes. For the digital input of the questionnaires, Research Manager® was used. Participants were asked to fill out a questionnaire and a Frequency Volume Chart (FVC).
The institutional review board of our hospital approved this study (nr 14.061).

Questionnaires

The questionnaire consisted of three parts: the validated International Consultation on Incontinence modular Questionnaires (ICIQ) [11, 12]; the MLUTS or FLUTS, for males and females, respectively, and the LUTSqol. MLUTS scores range from 0-20 (voiding symptoms), and 0-24 (incontinence); FLUTS scores range from 0-16 (filling), 0-12 (voiding), and 0-20 (incontinence).
The third part of the questionnaire consisted of questions concerning enuresis, developed by ourselves for this study. Although a questionnaire for evaluating nocturia, enuresis and quality of life exists (NNES-Q), this questionnaire has been validated in an elderly, unselected population [13]. Therefore, we believed that it consists of questions, which are not completely appropriate for our population. Additionally, NNES-Q has not been validated in Dutch. Consequently, we have chosen to compose a questionnaire with additional relevant questions, which are not addressed by the ICIQ's. These questions concerned the amount of wet nights, the severity of wetness, treatments after adapted DBT for enuresis, and current medication use.
The response rate for FVCs was expected to be lower than for the questionnaires. Therefore, at the first contact, we focused on these validated questionnaires and we sent the FVC's only to the responders of the questionnaires. We planned on contacting patients by telephone in case of a low response rate.

Initial power analysis and statistical analysis plan

Our purpose was to compare the prevalence of nocturia between patients who had an initial full response with those having had a partial or no response to adapted DBT. Therefore we performed a sample size calculation using this primary outcome parameter. Goessaert et al. found 35% of full response patients to have nocturia [6].

	Index population	Responders	Non-responders	Responders vs non-responders
Number, n (%)	553	76 (13.7)	477 (86)	
Gender, males, n (%)	361 (65)	41 (54)	320 (67)	*0.025*
Age in years, med [IQR]	22 [20-24]	23 [20-25]	22 [20-24]	*0.206*
Infrequent enuresis pre-treatment (≤3 wet nights/ wk), n (%)	176 (32)	28 (37)	148 (31)	*0.135*
Frequent enuresis pre-treatment (≥4 wet nights/ wk), n (%)	321 (58)	36 (47)	285 (60)	*0.135*
Treatment response after 6 months				*0.077*
no treatment response, n (%)	30 (7)	3 (6)	27 (7)	
partial treatment response, n (%)	114 (27)	8 (15)	106 (28)	
full treatment response, n (%)	283 (66)	43 (80)	240 (64)	

Table 1. Descriptives of patients, considering invitation and response.
Patients aged 18 years and older, and underwent adapted DBT ≥2 yrs ago were invited.
Analyses are performed by Chi-square, Fisher exact and Kruskall Wallis testing.

Between 2005 and 2011, 553 patients now aged 18 years and older were treated by adapted DBT and could be approached. With an expected response rate of 60%, 182 patients in each group would be available. With this amount of patients, we would have been able to demonstrate a difference of 14 percent in proportion of nocturia between the full and partial/no response group (α 0.05, β 0.2, two sided testing), which we considered to be clinically relevant.

Secondary study outcomes concerned current LUTS and micturition pattern, and quality of life, as measured with the ICIQ F and M LUTS and the ICIQqol, respectively. For quality of life assessment, a discrete 10-point scale was used. For the other items on the questionnaire, a Likert scale was used. These ordinal data are expressed in proportions. To compare the two groups, Chi-square testing was planned to be performed.

Adjustments to the study protocol

The response rate to the initial invitation was only 9% (n=48). Calling a subset of 89 patients, of which 48 patients were reached, resulted in a response rate of 15% (n=7). Therefore, a third effort was made, by resending the invitation to a random subset of 50 patients, which we offered a reward if the questionnaire would be completed. We wondered if our initial way of approaching patients was too difficult (giving them the choice of filling out the questionnaire digitally or asking for a paper questionnaire). Therefore, we chose to approach 25 patients of this subset the way we initially did, while the other 25 patients were immediately sent a paper questionnaire, without the opportunity of digital administration. As re-inviting all participants could be thought of to be unethical for the primary purpose of a study, we changed our focus from the initial primary outcome to potential solutions to improve response rates. As we received only one FVC, we decided not to describe these FVC data.

	Total	Initial invitation, digital	Initial invitation, paper	After calling	Second invitation (reward)	P
Number, n (%)	76 (13.7)	39	9	7	21	
Gender, males, n (%)	41 (54)	19 (49)	5 (56)	3 (43)	14 (67)	*0.541*
Age in years, med [IQR]	23 [20-25]	23 [22-25]	23 [22-25]	24 [20-25]	22 [19-24]	*0.585*
Infrequent enuresis pre-treatment (≤3 wet nights/ wk), n (%)	28 (37)	15 (38)	3 (33)	2 (29)	8 (38)	*0.993*
Frequent enuresis pre-treatment (≥4 wet nights/ wk), n (%)	36 (47)	18 (46)	4 (44)	3 (43)	11 (52)	*0.993*
Treatment response after 6 months						*0.117*
no response, n (%)	3 (6)	0 (0)	1 (20)	1 (25)	1 (6)	
partial response, n (%)	8 (15)	4 (14)	2 (40)	0 (0)	2 (13)	
full response, n (%)	43 (80)	25 (86)	2 (40)	3 (75)	13 (81)	
Nocturia (≥1x/ night), n (%)	48 (64)	27 (69)	6 (67)	5 (71)	10 (50)	*0.501*
Nocturia (≥2x/ night), n (%)	12 (16)	6 (15)	2 (22)	2 (29)	2 (10)	*0.653*
Bother score, males, med [IQR] (min-max)	1 [0-2] (0-10)	1 [0-1] (0-9)	0 [0-5] (0-10)	0 [0-1] (0-1)	1 [0-2] 0-7)	*0.475*
Bother score, females, med [IQR] (min-max)	1 [0-3] (0-7)	1 [0-4] (0-7)	2 [1-2] (1-2]	2 [0-4] (0-5)	0 [0-1] (0-5)	*0.506*

Table 2. Characteristics of response in different invitation phases.
Analyses are performed by Chi-square, Fisher exact and Kruskall Wallis testing.

	N (%)	Median [IQR]	Experienced as a problem (0 no- 10 big problem) Median (min-max)
Males	**41**		
ICIQ – symptom scores			
Voiding symptoms (0-20)	40	3 [1-4]	
Incontinence symptoms (0-20)	39	2 [1-4]	
ICIQ – specific questions			
Nocturia (≥1x)	22 (55)		0 (0-10)
Nocturia (≥2x)	3 (8)		
Urgency (sometimes/often)	23 ((58)		1 (0-10)
Perceived low self-image	7 (18)		0 (0-8)
Tired due to LUTS (sometimes/often)	7 (18)		0 (0-8)
Influence on sleep (sometimes/often)	16 (41)		0 (0-10)
Overall influence of LUTS on daily life			1 (0-10)
Additional questionnaire			
Enuresis (≥1 wet night/28 nights)	10 (30)		0 (0-10)
Enuresis (≥1 wet night/6 months)	16 (44)		
Frequent enuresis (≥4 wet nights/wk)	2		
Additional treatment after adapted DBT	1, mesology		
Females	**35**		
ICIQ – symptom scores			
Filling (0-16)	33	4 [2-5]	
Voiding symptoms (0-12)	33	1 [0-2]	
Incontinence symptoms (0-20)	34	3 [0.75-6.25]	
ICIQ – specific questions			
Nocturia (≥1x)	26 (72)		1 (0-10)
Nocturia (≥2x)	9 (25)		
Urgency (sometimes/often)	26 (74)		2 (0-8)
Perceived low self-image	11 (32)		0 (0-8)
Tired due to LUTS (sometimes/often)	13 (39)		0 (0-10)
Influence on sleep (sometimes/often)	21 (62)		2 (0-8)
Overall influence of LUTS on daily life			1 (0-7)
Additional questionnaire			
Enuresis (≥1 wet night/28 nights)	9 (28)		0 (0-10)
Enuresis (≥1 wet night/6 months)	20 (61)		
Frequent enuresis (≥4 wet nights/wk)	1		
Additional treatment after adapted DBT	3, PFP, botox, alarm		

Table 3. Results questionnaires, for males and females.
DBT: Dry Bed Training, ICIQ: International Consultation on Incontinence Questionnaire, PFP: Pelvic Floor Physiotherapy

Instead of comparing the prevalence of nocturia between initial treatment success groups (full response vs partial/no response), we decided to compare patient characteristics (age, gender, nocturia status, treatment response) according to the phase of responding (initial invitation, telephone reminder, reward), to see if invitation methods resulted in a different sample. We compared the differences between invitation groups by Chi-square and Kruskall-Wallis testing. Results of questionnaires are presented without further statistical analysis, for men and women separately (Table 3). Data were processed in SPSS 22.0.

Results

Response

An invitation to fill out the questionnaire was sent to 553 patients (65.3% males). Total response of

the three efforts was 14%. Response rate to the initial sending was 9% (n=48). The response rate to the additional calling of a subset of 89 patients of which 48 patients were reached, was 15% (n=7). The final subset of patients that was approached with a possibility of a reward gave a response of 42% (n=21 out of 50), of which 11 patients (44%) responded to the initial way of approaching - offering patients choice between digital and paper questionnaire- and 10 patients (40%) responded to the paper questionnaire.

Table 1 shows the distribution of age, gender, initial degree of enuresis and success group after six months for responders and non-responders. Overall, males were less likely to respond to the invitation (p=0.025). Responders seemed more likely to have had a full treatment response six months after adapted DBT, although this was not statistically significant (p=0.077). Table 2 shows these characteristics and current quality of life and nocturia, over the different invitation phases (initial sending/calling/reward). In the three invitation phases, there were no differences considering age or gender. The group of participants that responded to the invitation with the reward, seemed to have a lower prevalence of nocturia than the participants in the other groups, although this difference was not statistically significant.

ICIQ scores, nocturia and enuresis

Of the 76 responders, median age was 23 [IQR 20-25]. This represented 41 men and 35 women. ICIQ scores were all low (Table 3). Overall quality of life due to voiding complaints was median 1 (expressed on a Likert scale from 0-10), both for men and women. Nevertheless, maximum values were 7 and 10 respectively.

Nocturia (≥1 voids per night) was present in 55% of men and 72% of women; clinically relevant nocturia (≥2 voids per night) was present in eight percent of men and 25% of women. Enuresis (≥1/28 wet nights) was present in 10 (30%) of men and 9 (28%) of women (Table 3).

Discussion

Response

We faced serious problems in successful patient recruitment in studying long-term follow-up of treatment for enuresis. Comparable studies have experienced response rates of approximately 40% [6]. In a former short survey (unpublished data), we encountered a response rate of 47% of patients treated in the last ten years. However, from 2007 onward, the annual response rate was between 54 and 62%. Therefore, we had expected a higher response rate than we experienced in this study. The possibility of digital completion of the questionnaires was presumed to increase the response rate, as we approached a young, digitally active, group of patients.

Several different explanations for the problems in patient recruitment can be assigned: In daily life, people increasingly receive invitations to evaluate used services or products. Inevitably, this results in a lower willingness to participate in all separate evaluations. A more extensive questionnaire will have a negative impact on response rates. Our questionnaire was rather large. Additionally, patients had been asked to fill in a very short questionnaire before. The absence of an

active treatment relation with the DBBC may also negatively influence response rates in our view. Additionally, we evaluated a shameful problem; former patients want to let this topic rest if the enuresis is gone, or do not want to talk about it if it is still present. A high proportion of the responders had a full treatment response six months after the initial adapted DBT (80%). A full treatment response was defined following ICCS definitions as 100% response to treatment, so dry; no wet nights [7]. The full treatment response of the invited population as a whole was 66% (Table 1). This shows that mainly those patients that have been cured were willing to respond.

ICCS guidelines and Cochrane reviews focus on the lack of research on long-term follow-up and consequently propagate to report this information [7, 14]. As others have faced serious response problems as well, we doubt if long-term follow-up is feasible in this patient group, especially when patients do not have an active treatment relation with their physician anymore.

Different strategies to recruit patients

In this study, we used four different strategies to include patients. Our analyses showed differences in outcomes between these groups. Those patients that responded to the invitation with a reward differed with respect to the treatment response compared to the telephone group and the initial response on paper group. Although not statistically significant, a slightly lower proportion had nocturia. Of course, due to the low numbers, it is unclear whether this group or the other groups represent the whole population best. The initial responders could be eager to respond because they still have LUTS and are hindered by it. The responders to the reward-invitation are mainly those not experiencing any bother of their LUTS (median score 0, IQR 0-1). Possibly, their main reason for participation is the reward. Overall, we think it to be worthwhile to improve inclusion of patients by offering them a reward, as the response rate increased to above 40%, in which case additional analyses can be performed to interpret the data. There was no observed difference in response rate between offering patients choice between digital and paper questionnaire, and sending a paper questionnaire at once. No recommendations can be made for that specific topic.

ICIQ scores, nocturia and enuresis

In this paper, we decided not to present a sensitivity analysis, as the achieved response rate hampers the interpretation of such analyses. Response bias may well be present. The direction of the response bias is not clear but will most likely be directed toward a better quality of life and less LUTS, as full response to therapy patients were more likely to respond.

Conclusion

We faced serious problems in successful patient recruitment in studying long-term follow-up of adapted DBT for enuresis. As others have faced this as well, we doubt if long-term follow-up is feasible in this patient group. Possibly, only a prospective cohort study with a high emphasis on patient commitment could produce substantial and reliable long-term information. This is however, time consuming and costly. In case of gathering long-term follow-up in a retrospective study, we recommend to include a reward to increase response rates and thus interpretability of the results.

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CHAPTER 9

Summary, general discussion and future perspectives

This thesis has focused both on enuresis and nocturia, mutual causal factors like Nocturnal Polyuria (NP) and small Maximum Voided Volume (MVV), and on therapy for enuresis. In specific, the following topics were investigated: the association between NP and nocturia (part I), the wide variety of definitions of NP available for adults and children, and its consequences both for research and therapy (part I and II), evaluation of causal patterns of enuresis by frequency volume charts (FVCs) (part II) and on a treatment for and long-term evaluation of treatment-resistant adolescent and adult enuresis patients (part III). Here, a summary of the different topics of this thesis will be presented, combined with flaws and strengths of the specific chapters of this thesis, and future research perspectives.

Enuresis and nocturia - causal factors

Enuresis and nocturia share the causal triad of nocturnal polyuria, bladder storage problems and sleep problems. The overlapping causal factors probably show that the conditions are different entities in the same spectrum; the presence or absence of arousal to stimuli of the bladder makes that either enuresis or nocturia is present [1]. Sleep problems can be bidirectional related to nocturia: due to a voiding sensation and getting up to void, sleep is interrupted. On the opposite, people lying awake at night will often go for a convenience void [2]. Enuresis patients are superficial sleepers with an arousal problem. What the true cause of these arousal problems is remains unclear. Disturbed sleep is related to NP, via sleep deprivation, higher nocturnal blood pressure and lower AVP-levels [3].

NP is an overproduction of urine at night. It can be idiopathic due to aging, or can exist due to high evening fluid intake, disturbance of circadian pattern of atrial vasopressin (AVP), or a defect in AVP action. It can also be due to solute diuresis caused by congestive heart failure, sleep apnea or renal insufficiency [4]. In case of NP, after night-time fluid intake has been reduced, desmopressin can be prescribed [5-7]. Initially, desmopressin was mainly a treatment modality for enuresis. Currently, it is suggested as a treatment option in adults with nocturia as well [5]. Prescription data in the Netherlands show that it is much more frequently prescribed in children than in adults (Table 1). Additionally, over the years, it is slightly less prescribed (Table 2) [8].

A systematic review and meta-analysis on the efficacy and safety of desmopressin for adults showed that studies were of good quality but many studies did have a high risk of bias due to an active run-in period and exclusion of non-responders or patients with adverse effects. Desmopressin offers only a modest benefit for nocturia in healthy adults, by increasing the hours of uninterrupted sleep (one hour more than placebo), and slightly decreasing nocturnal voids (0.72 fewer voids

	0-4 yrs	5-14 yrs	15-24 yrs	25-44 yrs	45-64 yrs	65-74 yrs	≥75 yrs
Male	14	6162	1457	1152	1292	803	870
Female	21	2461	853	902	1363	563	670
Total	35	8623	2310	2054	2655	1366	1540

Table 1. Desmopressin use in the Netherlands in 2014 [8].

	2010	2011	2012	2013	2014
Desmopressin users	20771	20508	19754	18786	18584

Table 2. Desmopressin use in the Netherlands over the years [8].

compared to placebo) [9]. The main severe side-effects of desmopressin are headache (RR 4.3 vs placebo in nocturia patients) and hyponatremia (RR 5.1 vs placebo in nocturia patients) [9]. Hyponatremia is more often seen in the elderly, and leads to more clinically relevant situations in this group. The difference between adults and children in prevalence of hyponatremia as a side-effect of desmopressin use, could be explained by these different mechanisms. The pathogenesis in young patients is thought to be related to overdosing and insufficient fluid restriction [10]. In patients over 65 years of age, the pathogenesis is more related to a different renal water and solute handling [11]. Current guidelines state that desmopressin can be started when nocturnal polyuria is the main causal factor, as shown by the FVC, and non-pharmacologic treatment did not improve symptoms [7]. One of the problems however is the lack of a valid definition for NP, which is discussed on the following pages.

Reduced functional bladder capacity, or small MVV, is often caused by bladder storage problems, which can be due to overactive bladder (OAB), bladder outlet obstruction, neurogenic bladder, a high Post Void Residual volume, or developmental disturbances [4, 5, 12]. Other causes include dysfunctional voiding [1], cancer of the lower urinary tract, stones and aging [4]. OAB represents urge, urge-incontinence, increased frequency, nocturia and/or enuresis [1].

These three causal factors could potentially all be elicited by a distortion of parts of the brainstem, as the locus coeruleus, which has a function in sleep arousal, overlaps with the pontine micturition center and has connections with the AVP producing hypothalamus [13].
Others have investigated the relation between enuresis and nocturia in several ways. It was shown in a sample of mothers of children with enuresis, that those mothers who experienced enuresis in their own childhood, were at higher risk for having nocturia in adulthood [14]. Thirty-five percent of former enuresis patients in a tertiary care population had (clinically relevant) nocturia. This was mainly true for NMNE [15]. Nocturia was present in 75% of 25 enuresis patients when treated with desmopressin [16]. These studies however, all face problems regarding possible biases – recall bias in the study of the mothers, and selection bias in the tertiary care study. Additionally, the information is

Prevalence NP **5.0%**	Nocturnal Polyuria	No Nocturnal Polyuria	Total
Nocturia +	20	230	250
Nocturia -	30	720	750
Total	50	950	1000

Odds NP, nocturia +	(20/230)	
Odds NP, nocturia -	(30/720)	
Odds ratio NP	**odds NP nocturia + / odds NP nocturia -**	**2.09**
Risk NP, nocturia +	(20/250)	
Risk NP, nocturia -	(30/750)	
Relative risk NP	**risk NP nocturia + / risk NP nocturia -**	**2.00**

Prevalence NP **25.0%**	Nocturnal Polyuria	No Nocturnal Polyuria	Total
Nocturia +	100	150	250
Nocturia -	150	600	750
Total	250	750	1000

Odds NP, nocturia +	(100/150)	
Odds NP, nocturia -	(150/600)	
Odds ratio NP	**odds NP nocturia + / odds NP nocturia -**	**2.67**
Risk NP, nocturia +	(100/250)	
Risk NP, nocturia -	(150/750)	
Relative risk NP	**risk NP nocturia + / risk NP nocturia -**	**2.00**

Prevalence NP **60.0%**	Nocturnal Polyuria	No Nocturnal Polyuria	Total
Nocturia +	240	10	250
Nocturia -	360	390	750
Total	600	400	1000

Odds NP, nocturia +	(240/10)	
Odds NP, nocturia -	(360/390)	
Odds ratio NP	**odds NP nocturia + / odds NP nocturia -**	**26.00**
Risk NP, nocturia +	(240/250)	
Risk NP, nocturia -	(360/750)	
Relative risk NP	**risk NP nocturia + / risk NP nocturia -**	**2.00**

Table 3. Odds ratio's (OR) according to prevalence of nocturnal polyuria (NP).
In case of a constant relative risk (RR) of NP of 2.00, but a different prevalence of NP, the OR and RR are only comparable in the situation of a low prevalence. In case of a high prevalence of NP, OR and RR cannot be assumed to be similar. An OR can thus only be interpreted as an RR in case of a rare disease (Rare disease assumption). In this table, hypothetical numbers are used.

gathered retrospectively in former enuresis patients or their parents, resulting in missing information on the course of the enuresis.

Part I: Nocturnal polyuria, definition in and association with nocturia

A good definition of the conditions and the causal factors is important, not only to facilitate discussion and research initiatives, but also to decide when to start specific treatment, like e.g. desmopressin for NP. A is shown in Chapter 3, NP was found to be defined in 19 ways considering the adult population by different authors, studying the possible association between NP and nocturia. All these definitions used different strategies to calculate NP, and lack validation procedures. This lack of a validation procedure even accounts for the ICS and ICCS definitions, which are consensus-based [17, 18]. Nevertheless, the ICS does recommend to use their definition (adults: varying from young: nocturnal urine production >20% of total urinary production during 24h to elderly: >35%), which is also most frequently used. Clearly, due to all these different definitions, the true incidence and prevalence of NP is difficult to assess. Chapter 2 shows that the pooled prevalence, based on different NP definitions, is 63.8%. Most frequently, this was assessed by using an FVC. This is also the recommended method and has to include both voided volumes and (sleeping) times [18].

Chapter 2 also focuses on the association between nocturia and NP. It shows that nocturia and NP are indeed associated as was previously reported before by Weiss et al. [19]. However, the association is less firm than it seemed before: the relative risk of having NP for people with nocturia, compared to those without nocturia, (≥2x/night) is 1.41. However, current NP-definitions differentiate only moderately: the difference in nocturnal voids between people with and without NP is only 0.6 voids per night. This is most likely not clinically relevant. We also emphasized that odds ratios cannot be interpreted as relative risks when the prevalence of a condition is high. This refers to the rare disease assumption of the odds ratio (Table 3, Figure 1). It is probably one of the reasons why the association of nocturia and NP was previously thought to be much firmer.

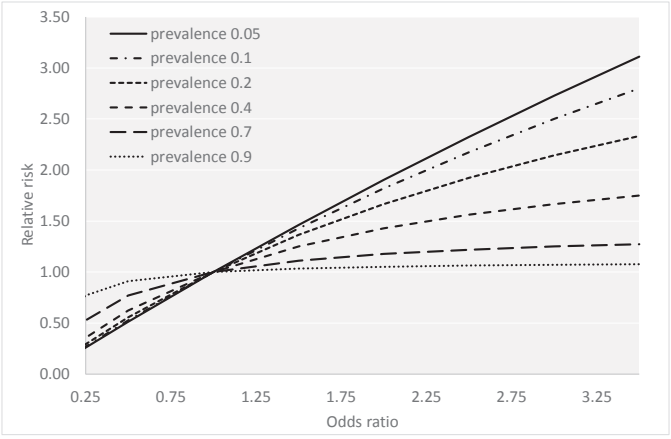

Figure 1. Relation Odds Ratio's and Relative Risks according to prevalence.
In case of a constant relative risk, but a different prevalence, the OR and RR are only comparable in the situation of a low prevalence. An OR can thus only be interpreted as an RR in case of a rare disease (Rare disease assumption).

Limitations of the systematic review and meta-analyses of part I (Chapter 2 and 3) are as follows: only 15 studies were available for meta-analyses, reflecting a restriction of this research field. Although language barriers did not result in exclusion of any of the studies found in Pubmed or Embase, it is possible that we have missed research in languages other than Dutch, English, French or German, which could have introduced selection bias.

Part II - *Nocturnal polyuria and bladder capacity, definitions in enuresis and assessment methods*
As stated, we have found 19 different definitions for adult NP in the literature. Even more intriguing is the fact that the definition is described in different ways by the two continence societies, the ICS for adults (varying from young: nocturnal urine production >20% of total urinary production during 24h to elderly: >35%) and the ICCS for children (ICCS NP-definition: >130% of the maximum EBC for age). Applying both definitions in our population of adolescents and adults with enuresis resulted in a striking different prevalence of NP (Chapter 4). Treatment choices will be based on presence of NP and will consequently inevitably vary between different definitions used.
Data regarding the exact prevalence of NP in patients with enuresis is lacking [20]. Due to enuresis episodes, nocturnal urine production measurement is difficult. This is also one of the main shortcomings of Chapter 4, in which the ICS and ICCS definition of NP are compared in adolescent and adult enuresis patients. To date, it is unclear whether enuretic adolescents, or even enuretic adults, have to be assessed according to the ICCS or the ICS definitions.
Chapter 4 additionally described reference values for FVC and uroflowmetry parameters for enuresis patients aged 11 years and older. Small functional bladder capacity (FBC) or maximum voided volume (MVV), has been defined for children as <65% of expected bladder capacity (EBC) [17]. EBC (in ml) has been defined as (age in years +1)*30, for children aged 4-12 years [21]. Reference values for adults have been described as well [22]. MVV clearly showed an association to LUTS severity [22]. MVV increases with age during childhood, and decreases with age in adulthood [20, 22]. The first voided volume in the morning (first morning void) is not included in this definition. MVV equals the EBC if the first morning void is excluded. If the first morning void is included, the MVV is 80-100 ml higher than the EBC [20]. We presented both the proportion of patients with small MVV including and excluding the first morning void, which obviously resulted in different proportions of small MVV in our population.

Chapter 5 describes the use of FVCs and uroflowmetries for the assessment of bladder capacity and shows that only in the range of 200-450 ml voided during uroflowmetry, results are comparable with the FVC. Therefore, for daily clinical purposes, uroflowmetry could be used to make a rough-cut estimation of the MVV, only in this range.

Limitations of part II (Chapter 4 and 5) are mainly due to the retrospective character of the study, the corresponding missing data and problems in the lay-out of and information about FVCs used in the DBBC. These FVCs did point out how to measure nocturnal urine production. However, sleeping and waking times were not routinely recorded in a standardized way. This is one of the omissions of the retrospective study design, and has been adjusted in daily clinical practice according to this study. Strengths consist of the observation of the difference of NP prevalence when using the two NP-

definitions, and of the publication of reference values, which were not available yet.

Future research directives for part I and II – Importance of new definitions
Both for pediatric NP and for adult NP, new definitions have been proposed: a nocturnal urine volume greater than 20 x (age + 9) ml (pediatric) [20], based on a population sample. And for adult NP a nocturnal urine production > 90 ml/hr [23].

Although we do agree that it is advisable to improve uniform use of definitions throughout the medical literature, we do feel that the current ICS definition should not be recommended. One of the problems with the current definition could be that it includes the first morning void. Although this urine is indeed produced during night-time, the NP-definition is less distinctive with regard to nocturia episodes. On the other hand, a NP-definition that does not take the first morning void into account, also has severe limitations. Such a definition does not incorporate all urine produced during night-time, and will only define NP for patients suffering from nocturia as other patients will not collect their urine during night-time. However, such a definition could be of use to differentiate between nocturia severity.

A recent report by the nocturia think tank of the International Consultation on Incontinence – Research Society also stated that more practical and clinically meaningful definitions of NP are needed [5]. Recently, an ICS/ICCS working group has been formed, focusing on the definitions for nocturia and NP. Hopefully, the ICCS and ICS will interactively come to an overall definition, which is applicable both for children and adults, both in enuresis and nocturia. This definition should mainly cover the production of urine during the night, as this is easier to interpret and shows what a nocturnal overproduction of urine actually is. Conditions to which a NP-definition would have to rely on are indeed that the definition should be based on urine production per time unit instead of on a day/night or night/24-hour ratio or a diurnal urine pattern, especially when the first morning void is included [5]. For the interpretation of resulting nocturia or enuresis, this can be combined with other measures like the nocturnal bladder capacity index (NBCi) [24]. NBCi is not useful for the analysis of explanatory factors of nocturia, because nocturia is mathematically already incorporated and consequently always related.
This new, most appropriate NP-definition which will focus on nocturnal urine production alone should be thoroughly investigated and validated in different populations (general population, primary/ secondary/ tertiary care). For this, raw FVC data from earlier studies could be used. Both in- and exclusion of volume of first morning void should be studied.

Altogether, several study designs of choice can be used to determine and study reference values of nocturnal urine production, and come to a new NP-definition. Examples are longitudinal cohort studies to assess reference values, and prevalence and incidence rates of NP, or cross-sectional studies for the assessment of reference values, defining of a new NP-definition, and prevalence of NP when using this definition. Ultimately case-control studies could investigate the distinctive nature of the definition in nocturia patients versus controls. The most appropriate method to gain information on urine production and on nocturia would be the frequency volume chart on which

sleeping times should be recorded, supplemented with a questionnaire, like the IPSS or the ICIQ.

Considering small MVV: we presented both the proportion of patients with small MVV including and excluding the first morning void, which obviously resulted in different proportions of small MVV in our population. Apparently, this first void is in general larger than the other voids during the day. Potentially, the circadian rhythm and physiology of sleeping, including the decreased sensation of a bladder stimulus during sleep, results in a larger volume of this first void. We feel that the volume of the first morning void is taken into account in clinical decision-making. It would be sensible to present both values in future research – MVV including first morning void and MVV excluding first morning void. Possibly, this is another topic for the ICS/ICCS committee. Here as well, studies should incorporate FVCs as the method of choice, and the distinctive nature of new definitions could be assessed with the same study designs as proposed for the new definition of nocturnal polyuria.

Circadian rhythm and sleep in enuresis and nocturia

Although not the primary subject of this thesis, one of the additional interesting fields of study in the area of enuresis and nocturia is the circadian clock mechanism. The multifactorial etiology of both enuresis and nocturia is possibly related to this mechanism. Hypertension, diabetes and depression often occur together, in the presence of nocturia. In genetically modulated mice with a dysfunctional circadian clock, the diurnal rhythm of micturition, production of urine and functional bladder capacity is lost [25]. Micturition cycle disorders like enuresis and nocturia could be genetic and present itself throughout the life span [25]. Related to this, a seasonal variation in nocturia symptom severity in men with LUTS exists; in winter, there were less nocturia events [26]. Seasonal variation does also exist in enuresis, at least for treatment success of alarm therapy, for which winter was shown to be associated with failure [27]. And, although melatonin has a circadian rhythm; serum levels are high at night and low during the day, and is associated with sleep, it is not with enuresis. Enuresis and control patients however had no different melatonin levels [28], and melatonin treatment in therapy-resistant enuresis patients did not improve enuresis frequency [29].

As stated, the origin of the arousal problem in enuresis patients remains unclear. NP, sleep deprivation, nocturnal hypertension and AVP-levels are interrelated [3], and the underlying problem could be based in the brainstem [13]. Sleep studies and studies focusing on the neurological basis of arousal could be of help to further distinguish these two entities [1]. Additionally, radiographic or nuclear studies could be initiated to compare activity in these brain-regions between enuresis patients and controls, between enuresis patients and nocturia patients, and between sleep deprivation and no sleep deprivation.

Part III - Therapy-resistant enuresis in adolescents and adults, adapted Dry Bed Training (DBT)

The initial treatment of enuresis is clear and consists of alarm therapy and/or desmopressin [7, 12]. Those treatments are known to be helpful during treatment, but have a high relapse rate. Recently, imipramine has been advocated as the next therapeutic step for patients who are treatment-resistant, although it has adverse effects like cardiac problems, personality

changes, insomnia, anorexia and anxiety [30, 31]. Still, after alarm therapy, desmopressin and imipramine were applied in adolescent patients, 17% remained therapy resistant [32]. Specifically for the group of patients which are 11 years and older and therapy-resistant to alarm therapy and desmopressin, adapted DBT has been developed in 2003 by a urologist, continence nurse and the patient association. Part III of this thesis focuses on this adapted DBT for therapy-resistant enuresis in adolescents and adults. In our retrospective analyses, we showed that adapted DBT seems to be effective in a large group of therapy resistant patients. Although the exact place of adapted DBT remains to be determined, it could be an option for treatment-resistant adolescents and adults (Chapter 6). To improve the interpretation of the data with regard to the missing data that we encountered, we chose to present sensitivity analyses in this chapter. The worst-case and best-case scenario showed that the real treatment success would be within wide limits, but at least 43% after six months. However, due to the retrospective study design and the lack of a control group, no definite recommendations can be made.

Given the costs, it is interesting to identify those patients that benefit most. This discussion on costs is comparable to what could be read in the early papers on DBT as well [33, 34]. Nevertheless, back then, DBT was performed as a first-line treatment as well, whereas it now seems more appropriate to direct adapted DBT only to therapy-resistant cases. To identify the patients that are susceptible for treatment success, we performed prediction modeling to identify patient factors predicting success in Chapter 7. We showed that there are several factors that are involved in success of adapted DBT. Although the temptation is present to elucidate why these factors are found to be predictive, it is good to remember that no causal relationships can be inferred based on prediction models. Due to the low explained variance of our model, we expect many other factors to be involved as well. Bladder capacity will be one of them. One of the inclusion criteria for the adapted DBT was an FBC of 300 ml or more. Therefore, this factor could not be studied. The intensive relation with the pedagogic staff could have been a positively influencing factor as well; it is known that contact with a therapist is helpful. It enhances the effect of an intervention [35, 36]. Possibly, this and explicit agreements are of additional value in patients with behavioral problems like ADHD. Additionally, the low explained variance could be due to the homogenous group of patients that were treated, and the high proportion of success, resulting in low predictive possibilities.

Overall limitations of Chapters 6 and 7 are the retrospective design, and the missing data encountered. In Chapter 6 we chose for the neat observation that a sensitivity analysis offers, to be able to deliberate on reasons for the real results being closer to the worst or best case analysis. Besides, we felt that this is easier to interpret for clinicians in general. For the additional regression analyses of Chapter 7 however, we needed to improve the reliability of our database. Therefore, we performed multiple imputation before running the logistic regression analyses. This way, we were able to strengthen our conclusions.

In Chapter 8, we investigated long-term follow up of the adapted DBT. Larger sample sizes and longer follow up are advocated by Cochrane reviews and the ICCS [17, 35]. However, a quick review of the literature reveals that only a few studies indeed have had a follow up longer than 1 year. One study investigating the body worn alarm and a supportive program in 505 monosymptomatic enuresis

patients achieved a follow up of 99.2% after two years [37]. Nevertheless, this is a rare example. Much more often, response rates for long term follow up studies are around 40%, like the Gent group experienced [15]. We experienced even lower response rates (Chapter 8). We performed a cross-sectional study to gain knowledge on the long-term follow up of enuresis patients treated by adapted DBT, specifically on nocturia and associated quality of life. This appeared to be very difficult, and we changed our focus to the question how to improve response rates in this population. Offering a reward for a completed questionnaire gave a higher response rate, although this was still only moderate (42%). Potential reasons are the overload on questionnaires sent by (commercial) entities; increasingly causing a feeling of bother and the lack of feeling that one can be of added value. Additionally, patients are not patients anymore; there is no actual treatment-relationship, and therefore it seems less interesting for people to join.

Future research directives for part III

Future research on adapted DBT would preferably be prospective. A prospective randomized trial could hardly include placebo treatment, although sham-treatment would be possible. Nevertheless, it is difficult to define what the sham-arm should and should not include. Adapted DBT versus no treatment will not be ethically justified and feasible, as we sincerely question whether these patients would be willing to join such a study. A possible future study could be to investigate the effect of adapted DBT of five days and four nights versus a shorter period of time (the sham-arm). This will also address the main problem of adapted DBT; which are the high costs that are involved. In fact, the current adapted DBT in our center has already been shortened to four days and three

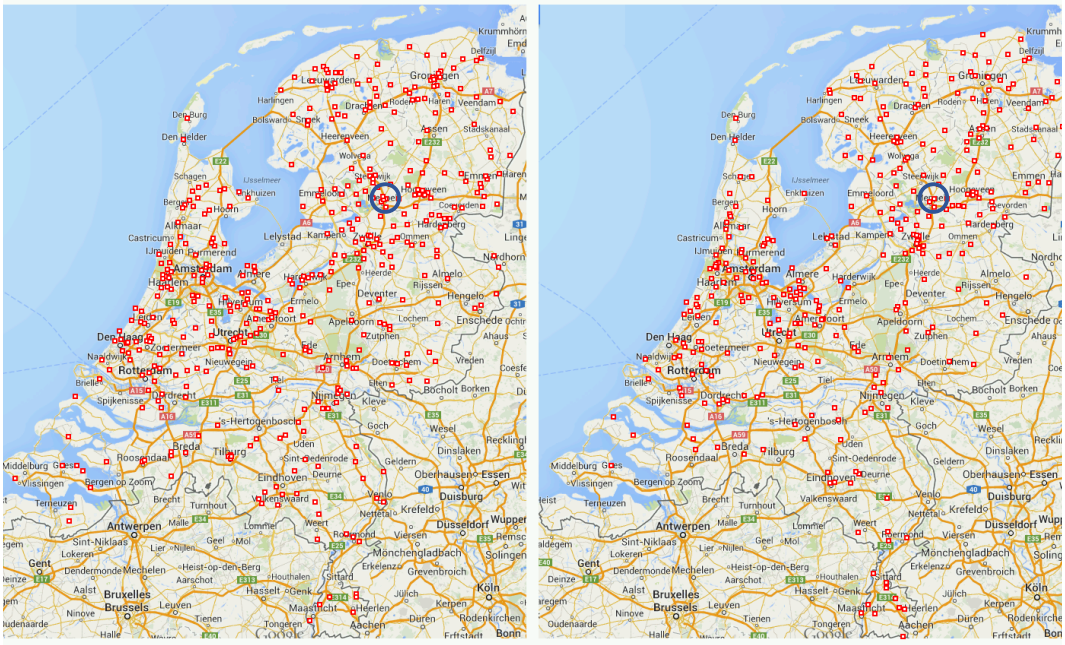

Figure 2. Origin of patients treated by adapted Dry Bed Training.
Red squares represent place of residency of treated patients, based on postal code.
Blue circle represents Dry Bed and Pelvic Center.
Left: 2003-2008. Right: 2009-2013.

nights, among other things due to costs. Therefore, we already started a prospective cohort study in patients currently treated by this shortened in-hospital training. The fourth night is performed at home, with extensive telephone contact in the evening and the next morning. Here, the data-handling is improved not only due to the prospective character, but also due to the faced difficulties and shortcomings of the historical cohort, resulting in improved maintaining of medical charts for study purposes. In the future, this cohort can be compared to the historical cohort that is described in Chapter 6 and 7.

For prediction modeling, all data that are available for the clinical setting, could be used. In other fields of medicine, like oncology, it is widely acknowledged that insight in current treatments can only be gained by recording patient data in a thorough way. In our center, we started prospective data recording of all consecutive outpatients treated for enuresis in 2015. For this we have defined several quality parameters, which will be assessed twice a year, to improve overall patient care.

Other developments in medicine are the number of cases treated that has to overcome a certain threshold, to gain skills and knowledge in a particular center (volume-standards). In children, enuresis is a highly prevalent condition and thus many healthcare professionals nearby home should perform treatment. However, in adolescents and adults, particularly the therapy-resistant cases are not that frequently encountered by a general practitioner or even a urologist. Therefore, we advocate that there should be only a few centers that satisfy volume-standards, direct this treatment and have the skills and knowledge available. In that light, the Dry Bed and Pelvic Center is a unique treatment facility. This has been shown by the numbers of patients in this age group that were treated during the last decade, from all over the Netherlands (Figure 2). It is important to keep improving the available knowledge and treatment modalities for this difficult to treat, but interesting group of patients.

Summary and additional remarks

Future directives for research have been described throughout this discussion and focus mainly on the causal factors of enuresis and nocturia and their definitions, on transition in urology, on therapy-resistance and initiatives to improve long-term follow-up.

During the years of this PhD research, the research group on enuresis from Gent, Belgium, has also studied the relation between enuresis and nocturia, and nocturnal polyuria [1, 15, 38]. The renal function profile that they have investigated seems to be interesting for future research on nocturnal polyuria both in nocturia and enuresis [38]. It differentiates between water and solute diuresis and can indeed be of help to determine the best treatment modality. Possibly, this explains the non-response in some children with nocturnal polyuria to desmopressin. Additionally, they also studied long-term follow up of enuresis patients, and encountered low response rates, like we did. Altogether, many thoughts on the subjects have been comparable. Although we first wondered if sensitivity analyses should be performed to account for the missing data in their sample [39], since we have experienced even lower response rates, we should join forces to come to solutions to improve long-term follow up of enuresis patients.

In general, many things remain elusive considering enuresis in adolescents and adults. It is not only often therapy-resistant, another subset of patients is known to never even have consulted a doctor for their complaints [40]. It however is known that those patients who remain wet if they grow older, have more severe complaints [41]. Therefore, it is of utmost importance that patients are identified and treated, as 'healthy aging starts the moment you're born'.

In conclusion: this thesis has shown that, although the association between nocturia and NP is apparent and robust, definitions of NP are widespread and differing, both for children and adults. Epidemiologic measures like odds ratio and relative risk should be interpreted according to the prevalence of disease. It has also shown that, in adolescents and adults with treatment resistant enuresis, adapted DBT gives good results, although the exact place of adapted DBT is not clear yet. Furthermore, long-term follow up was found to be difficult to assess in this group of patients, and could be improved by prospective cohort studies, or introducing a reward for completion of questionnaires. The research field of these entities should become more integrated than it currently is. The two continence societies could play an important role in this, for a start by discussing their non-conform definitions together and to come to uniform points of view, not the least because adolescents should not fall between two stools, between pediatric and adult urology.

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CHAPTER 10

Nederlandse samenvatting

Dit proefschrift bespreekt verschillende aspecten van enuresis (bedplassen) en nycturie (wakker worden om te plassen), nachtelijke plasproblemen met een vergelijkbare pathofysiologie.

Hoofdstuk 1 introduceert beide ziektebeelden, inclusief terminologie, etiologie, epidemiologie en effect op kwaliteit van leven. Tevens worden huidige behandelingen besproken. Nachtelijke polyurie, een kleine blaascapaciteit en slaapproblemen komen bij beide ziektebeelden voor.

Nachtelijke polyurie betreft een overmatige productie van urine gedurende de nacht. De urine-productie wordt onder andere gereguleerd door atriaal vasopressine (AVP). Hierdoor blijft de plasma-osmolariteit en natrium concentratie gehandhaafd. Kleine aanpassingen in de hoeveelheid AVP kunnen een groot effect hebben op de hoeveelheid vocht die uitgescheiden wordt. Normaliter heeft zowel de secretie van AVP als de productie van urine een 24-uurs ritme; 's nachts wordt er minder urine geproduceerd. Nachtelijke polyurie kan optreden als het 24-uurs ritme van AVP secretie verstoord is. Andere oorzaken zijn een overmatige vocht-intake gedurende de avond, hartfalen, slaap apneu en nierfalen. AVP secretie wordt daarnaast beïnvloed door veroudering.

Nachtelijke polyurie wordt verschillend gedefinieerd door de twee wetenschappelijke continentie verenigingen. De definitie van de International Continence Society (ICS – volwassenen) en de International Children's Continence Society (ICCS – kinderen) worden respectievelijk bij nycturie en bij enuresis toegepast. De ICS definitie is als volgt: een leeftijdsafhankelijke nachtelijke urine output groter dan 20-33% van de 24-uurs urine output: de nachtelijke polyurie index. De ICCS definitie gaat niet uit van deze ratio, maar van het concept dat de nachtelijke urine productie de verwachte blaascapaciteit voor de leeftijd overschrijdt: indien de nachtelijke urineproductie meer dan 130% van de verwachte blaascapaciteit is, is er sprake van nachtelijke polyurie. Het is duidelijk dat deze twee definities een andere insteek hebben.

Blaascapaciteit betreft de hoeveelheid urine die de blaas kan opslaan. Ook de blaascapaciteit heeft een 24-uurs ritme: de eerste plas van de dag is groter dan alle andere. Tot de leeftijd van 12 jaar neemt de blaascapaciteit toe, en naarmate volwassenen ouder worden neemt deze weer af. Er zijn meerdere manieren om de blaascapaciteit te meten: cystometrie al dan niet onder anesthesie, uroflowmetrie of het plasdagboek (Frequency Volume Chart – FVC). Mogelijke oorzaken van een verminderde functionele blaascapaciteit zijn opslagproblemen zoals onder andere outlet obstructie, overactieve blaas, een groot residu of een neurogene blaas.

Slaapproblemen zijn vermoedelijk verschillend bij enuresis en nycturie. Bij enuresis is er voornamelijk een ontwaakprobleem. Bij nycturie is het lastig te objectiveren wat het primaire probleem is; een slaapstoornis waardoor een persoon gaat plassen, of juist een plasprobleem waardoor de slaap wordt onderbroken.

Het doel van dit proefschrift is het bestuderen van verscheidene aspecten van deze twee ziektebeelden. Hierbij wordt ingezoomd op een aantal zaken: de associatie met nachtelijke polyurie, huidige definities en ten slotte aangepaste droog bed training bij behandel resistente adolescente en volwassen enuresis patiënten.

Deel I - Nycturie en nachtelijke polyurie
Dit deel omvat een systematische review en meta-analyse naar de associatie tussen nycturie en nachtelijke polyurie, met een beoordeling van de interne en externe validiteit, informativiteit en het effect van de publicatie van het ICS standaardisatie rapport over terminologie.

Hoofdstuk 2 toont aan dat nycturie en nachtelijke polyurie inderdaad geassocieerd zijn, zoals eerder reeds werd beschreven. Deze relatie is echter minder stevig dan tevoren werd aangenomen. Mensen met nycturie (≥2x/nacht) hebben, in vergelijking met diegenen zonder klinisch relevante nycturie, een relatief risico van 1,41 op nachtelijke polyurie. De eerder vermoede steviger associatie komt waarschijnlijk doordat eerder de hoge prevalentie van nachtelijke polyurie niet is meegenomen in de berekeningen. De hoge odds ratio (4,99 in Hoofdstuk 2) komt overeen met een lager relatief risico in verband met de hoge gepoolde prevalentie van 63,8%; er is dus geen sprake van een zeldzame ziekte (Tabel 3 en Figuur 1 Hoofdstuk 9), waardoor de odds ratio niet als een relatief risico kan worden geïnterpreteerd. Wanneer de relatie andersom wordt bekeken blijkt dat, indien er sprake is van nachtelijke polyurie, dit samengaat met slechts 0,6 plassen per nacht meer dan indien er geen sprake is van nachtelijke polyurie. Dit verschil is vermoedelijk niet klinisch relevant.

In de medische literatuur voor volwassenen blijken in ieder geval 19 verschillende definities voor nachtelijke polyurie in omloop. In Hoofdstuk 3 wordt beschreven dat veel van deze definities verschillende methoden gebruiken om nachtelijke polyurie te berekenen. Daarnaast ontbreken validatie procedures, zelfs voor de ICS en ICCS definities. De publicatie van het ICS terminologie standaardisatie rapport in 2002 bleek een positief effect te hebben op het rapporteren van gebruikte definities. De ICS definitie wordt het meest gebruikt. Het belang van eenduidige, goede definities is helder: het duiden van de precieze prevalentie en incidentie van nachtelijke polyurie is op dit moment lastig vanwege de verschillende maatstaven waarmee gemeten wordt.

Deel II – Enuresis, nachtelijke polyurie en functionele blaas capaciteit: focus op definities
Naast alle definities die gevonden werden voor volwassen nachtelijke polyurie, is het intrigerend om op te merken dat ook de ICS en de ICCS definitie van nachtelijke polyurie verschillend zijn. Ze zijn gebaseerd op verschillende concepten. Het is onduidelijk of adolescente en jongvolwassen patiënten met enuresis geëvalueerd moeten worden volgens de ICS of juist volgens de ICCS definitie. Dit is interessant, aangezien de prevalentie van nachtelijke polyurie zeer verschillend bleek te zijn wanneer de ene of de andere definitie werd toegepast (Hoofdstuk 4). Indien patiënten op de dag dat ze 18 jaar worden volgens de volwassen definitie moeten worden geëvalueerd, zullen veel van hen van de ene op de andere dag nachtelijke polyurie (lijken te) hebben. Dit is van belang omdat behandelkeuzes hierop gebaseerd kunnen en zullen zijn.

Samenvattend is het essentieel dat de twee wetenschappelijke verenigingen samen tot een nieuwe definitie komen. Inmiddels is zowel voor kinderen als voor volwassenen een nieuwe definitie van nachtelijke polyurie voorgesteld. Deze voorgestelde definities gaan beiden uit van alleen de nachtelijke urine productie. Er is een commissie samengesteld uit ICS en ICCS-gelederen, die zich buigt over deze kwestie. De nieuwe nachtelijke polyurie definitie is pas optimaal indien deze goed gevalideerd wordt in verschillende populaties. Plasdagboek data van eerdere studies kunnen hier

goed voor worden gebruikt, waardoor de tijdspanne tot het bereiken van deze valide definitie verkort kan worden.

In Hoofdstuk 4 worden daarnaast referentiewaarden voor plasdagboek en uroflowmetrie parameters beschreven voor adolescente en volwassen enuresis patiënten. Bij gebruik van de ICCS definitie om het maximaal geplast volume te berekenen, wordt de eerste ochtendplas buiten beschouwing gelaten. Wij kozen ervoor om het maximaal geplast volume op twee wijzen te presenteren: met en zonder meenemen van de eerste ochtendplas.

Hoofdstuk 5 betreft een post-hoc analyse naar twee meetmethoden voor blaascapaciteit. Het maximaal geplast volume van het plasdagboek (zonder eerste ochtendplas) werd vergeleken met het geplaste volume bij uroflowmetrie. Deze analyse suggereert dat, wanneer een patiënt bij uroflowmetrie een volume plast van 200-450 ml, dit resultaat vergelijkbaar is met het maximaal geplast volume van het plasdagboek. Alleen in dit bereik kan uroflowmetrie gebruikt worden om een grove schatting te maken van het maximaal geplaste volume.

Deel III – Adolescenten en volwassenen met enuresis: aangepaste droog bed training

De aanvankelijke behandeling van enuresis is duidelijk en bestaat uit alarm therapie en/of desmopressine, afhankelijk van de aanwezigheid van een kleine blaascapaciteit of nachtelijke polyurie. Het is bekend dat beide opties goed werken tijdens de behandeling, maar een hoog terugval percentage hebben wanneer de behandeling wordt gestopt. In 2003 werd speciaal voor de groep patiënten van elf jaar en ouder die therapie resistent waren voor alarm therapie en desmopressine, een aangepaste vorm van droog bed training (DBT) ontwikkeld in het Droog Bed en Bekken Centrum te Meppel. Deel III van dit proefschrift richt zich op deze aangepaste DBT, welke plaats vindt gedurende vijf dagen en vier nachten in leeftijdsgroepen van zes patiënten. De training omvat een enuresis-anamnese, uitleg over de ziekte, gebruik van een dagboek, een plaswekker en een eigen gewone wekker, groepscontact en activiteiten gedurende de dag om het zelfvertrouwen van de deelnemers te vergroten. De nacht wordt zowel 's avonds als 's ochtends met de deelnemers besproken. De eerste nacht worden deelnemers elk uur gewekt om te voelen of ze moeten plassen en om een glas water te drinken. De daaropvolgende nachten slapen ze met de plaswekker en met een eigen wekker die 's nachts op een geïndividualiseerd tijdstip wordt gezet. Behandeling is multidisciplinair: de training wordt uitgevoerd door pedagogisch medewerkers. Uroloog en continentie verpleegkundigen zijn tevens betrokken. Follow up wordt telefonisch verricht; de eerste zes weken gebeurt dit wekelijks, waarna de frequentie wordt afgebouwd tot zes maanden na de training. De plaswekker wordt gecontinueerd na de klinische training en wordt gestopt als patiënten twee weken droog zijn.

Hoofdstuk 6 en 7 betreft een retrospectief cohort onderzoek, waarbij in Hoofdstuk 6 de behandeling en de resultaten van deze behandeling worden besproken. In verband met ontbrekende data werd een sensitiviteitsanalyse uitgevoerd. Na 6 weken bleek 46% van de patiënten een volledige behandelrespons te hebben: zij waren 's nachts droog. Het werkelijke succes percentage zal liggen tussen de twee scenario's van de sensitiviteitsanalyse: 31% en 64%. Het behandelsucces na 6 maanden was 68% in de beschikbare data en lag volgens de sensitiviteitsanalyse tussen 43% en 80%.

Vanwege de kosten is het interessant om na te gaan welke patiënten het meeste profijt hebben van de aangepaste DBT. Derhalve focust Hoofdstuk 7 op een predictiemodel waarin patiënt-factoren worden betrokken die succes voorspellen. Vanwege de ontbrekende data werd multipele imputatie toegepast voordat een logistische regressie analyse werd verricht. Er bleken meerdere factoren te kunnen worden geïdentificeerd. Externe validatie dient echter plaats te vinden voordat dit model gebruikt kan worden. Een nadeel van dit model is de lage verklaarde variantie, waardoor andere factoren mede van belang zullen zijn voor succes.

De ICCS beveelt aan om patiënten tot twee jaar na behandeling te volgen. Dit lijkt gezien de hoge terugval percentages na conventionele behandelingen als plaswekker en desmopressine ook verstandig, zodat het uiteindelijke effect van de behandeling ingeschat kan worden. In Hoofdstuk 8 wordt een cross-sectionele vragenlijst studie gepresenteerd, waarbij zeer lage respons percentages werden verkregen. Vragenlijst studies lijken in zijn algemeenheid gepaard te gaan met een tegenvallende respons. De vraag dringt zich op op welke manier de uiteindelijk beschikbare data geanalyseerd en de resultaten geïnterpreteerd moeten worden. We hebben de focus van dit hoofdstuk vanwege deze tegenvallende respons aangepast naar de vraag op welke manier we de respons konden verbeteren. Hoewel er meer vragenlijsten werden ingevuld bij het aanbieden van een beloning, bleef de respons mager (42%). Mogelijke verklaringen voor de tegenvallende respons zijn de hoeveelheid vragenlijsten die dagelijks per e-mail binnenkomen, het feit dat enuresis een aandoening is die gepaard gaat met schaamte, evenals het feit dat patiënten geen actuele behandelrelatie meer hadden.

Hoewel aangepaste DBT succesvol lijkt te zijn in de voorheen therapieresistente groep enuresis patiënten, is voorzichtigheid bij het trekken van conclusies op zijn plaats vanwege het retrospectieve karakter van de studie, het ontbreken van een controle groep en de matige respons op de vragenlijststudie naar plasklachten langere tijd na behandeling.

Toekomstig onderzoek zou daarom gericht moeten zijn op het prospectief vergelijken van de aangepaste DBT met bijvoorbeeld een sham-arm, of een verkorte versie van de training. Dit is ook uit kostenoverwegingen interessant. Ook een historische vergelijking behoort tot de mogelijkheden. De huidige training omvat 4 dagen en 3 nachten. De vijfde nacht wordt thuis geslapen. ’s Avonds en ’s ochtends is er telefonisch contact met de pedagogisch medewerkers. Alle patiënten die worden gezien op het Droog Bed en Bekken Centrum, worden prospectief geëvalueerd. Dit prospectieve cohort is gestart om de kwaliteit van zowel proces als behandeling te verbeteren; kwaliteits-prestatie indicatoren zijn vastgesteld, welke halfjaarlijks geëvalueerd worden. Dit cohort kan in de toekomst vergeleken worden met het historische cohort uit Hoofdstuk 6 en 7.

Tenslotte biedt dit proefschrift plaats voor de discussie over volume-normen in de klinische praktijk. Enuresis is een veelvoorkomend probleem bij kinderen waardoor zorg dicht bij huis beschikbaar moet zijn. Echter, enuresis komt ook voor bij 0,5 tot 2% van de adolescente en volwassen populatie. Deze patiënten zijn vaak therapie resistent en hebben ernstiger enuresis. Voor deze groep patiënten lijkt centralisatie verstandig: het aanwijzen van enkele centra voor behandeling, waardoor kennis en kunde gezekerd zijn.

Concluderend toont dit proefschrift dat, hoewel de associatie tussen nycturie en nachtelijke polyurie bestaat, deze minder sterk is dan tevoren werd aangenomen. Bij het omzetten van een odds ratio naar een relatief risico is het van belang om de prevalentie van ziekte mee te nemen. Daarnaast blijkt nachtelijke polyurie vele gezichten te hebben: in de volwassen literatuur in ieder geval op 19 verschillende wijzen gedefinieerd, en door de volwassen en kinder-wetenschappelijke continentie verenigingen ook verschillend gedefinieerd. Hierdoor is de werkelijke prevalentie van nachtelijke polyurie lastig in te schatten.

Aangepaste droog bed training geeft goede resultaten bij adolescenten en volwassenen met voorheen behandel-resistente enuresis, hoewel de precieze plaats van deze training in het behandelspectrum nog niet duidelijk is. Het was lastig om informatie te verkrijgen over de resultaten op langere termijn. Dit kan verbeterd worden door prospectieve observationele cohort studies of door een beloning aan te bieden bij het invullen van vragenlijsten.

Kennis over deze twee nachtelijke plasproblemen lijkt gebaat te zijn bij de integratie van de twee onderzoeksgebieden. De twee continentie verenigingen kunnen hier een belangrijke rol bij spelen, bijvoorbeeld door tot gezamenlijke definities en standpunten te komen. Hierbij is niet alleen het wetenschappelijk onderzoek gebaat, maar vooral ook de patiënt, wanneer die van kind volwassene wordt.

CHAPTER 11

Curriculum vitae

Publications

Dankwoord

Curriculum vitae

Ilse Hofmeester was born in Apeldoorn on March 6th, 1985 as the eldest of three daughters of Fred Hofmeester and Carla Melisie. She finished pre-university education at the Gymnasium Apeldoorn in 2003 and started medical school at the Rijksuniversiteit Groningen. She did her rotations at the University Medical Center Groningen, Wilhelmina Ziekenhuis Assen and Medisch Spectrum Twente, Enschede. For her research internship, she went to Flinders University in Adelaide, Australia to study the molecular, physiological and pharmacological basis of contractility in isolated specimens of human and guinea pig colon in vitro. Her elective internship was spent at the department of abdominal surgery and the department of internal medicine – kidney transplantation at the University Medical Center in Groningen. She graduated as a Medical Doctor in 2010.

After finishing medical school, she started working in the department of urology of the Ziekenhuis Groep Twente in Almelo and Hengelo. Subsequently, she worked in the department of urology of the Isala in Zwolle. She started her fulltime PhD program in Zwolle in July 2013, as an external PhD-candidate of the Radboud University Nijmegen. During this period, she also followed a Master in Clinical Epidemiology at the Erasmus University in Rotterdam. Ilse started her urology residency program in cluster Groningen in January 2016.

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Dankwoord

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